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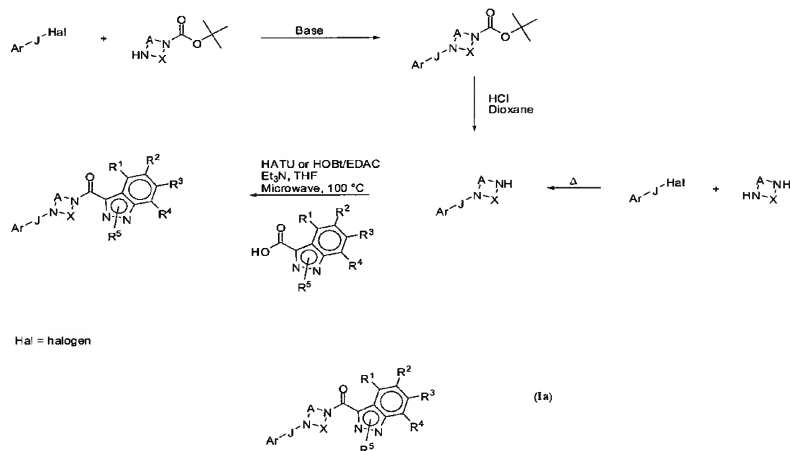
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(54) Title: INDAZOLE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO



(57) Abstract: Indazole derivatives of Formula (1a) and pharmaceutical compositions thereof that modulate the activity of the serotonin 5HT_{2A} receptor. Formula (1a) Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia and related sleep disorders, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy and the like. The present invention also relates to the methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.



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**INDAZOLE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} SEROTONIN
RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED
THERETO**

5 **FIELD OF THE INVENTION**

The present invention relates to certain indazole derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the 5-HT_{2A} serotonin receptor. Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia and related sleep disorders, platelet aggregation, coronary artery
10 disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related
15 disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy and the like.

The present invention also relates to the methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.

20 **BACKGROUND OF THE INVENTION**

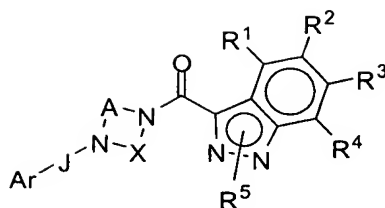
Serotonin receptors

Receptors for serotonin (5-hydroxytryptamine, 5-HT) are an important class of G protein coupled receptors. Serotonin is thought to play a role in processes related to learning and memory, sleep, thermoregulation, mood, motor activity, pain, sexual and aggressive behaviors, appetite,
25 neurodegenerative regulation, and biological rhythms. Not surprisingly, serotonin is linked to pathophysiological conditions such as anxiety, depression, obsessive compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism, and neurodegenerative disorders.

Serotonin receptors are divided into seven subfamilies, referred to as 5-HT₁ through 5-HT₇, inclusive. These subfamilies are further divided into subtypes. For example, the 5-HT₂ subfamily is divided into three receptor subtypes: 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}. The human 5-HT_{2A} receptor was first isolated and cloned in 1990.
30

SUMMARY OF THE INVENTION

One aspect of the present invention encompasses certain indazole derivatives as shown in
35 Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl, cyano, C₁-C₆ haloalkoxy, halogen and heteroaryl; and wherein C₁-C₆ alkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C₁-C₆ acyl, C₁-C₆ acyloxy, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ alkylureyl, C₁-C₆ alkylamino, C₂-C₆ alkynyl, amino, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylamino, C₂-C₆ dialkylcarboxamide, C₂-C₆ dialkylsulfonamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, C₁-C₆ haloalkylthio, halogen, hydroxyl, nitro, sulfonamide and thiol;

R^5 is selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ alkyl, arylcarbonyl, arylsulfonyl, C₃-C₇ cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

A and X are each -CH₂CH₂-, and each optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C₁-C₄ alkoxy, C₁-C₃ alkyl, carboxy, cyano, C₁-C₃ haloalkyl, halogen, hydroxyl and oxo;

J is -CH₂CH₂- optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C₁-C₄ alkoxy, C₁-C₃ alkyl, carboxy, cyano, C₁-C₃ haloalkyl, halogen, hydroxyl and oxo; and

Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C₁-C₆ acyl, C₁-C₆ acyloxy, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ alkylureyl, C₁-C₆ alkylamino, C₂-C₆ alkynyl, amino, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylamino, C₂-C₆ dialkylcarboxamide, C₂-C₆ dialkylsulfonamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, C₁-C₆ haloalkylthio, halogen, hydroxyl, nitro, sulfonamide and thiol.

One aspect of the present invention pertains to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

One aspect of the present invention pertains to methods for treating 5-HT_{2A} mediated disorders in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5 One aspect of the present invention pertains to methods for treating 5-HT_{2A} mediated disorders selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10 One aspect of the present invention pertains to methods for treating sleep disorders in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

 One aspect of the present invention pertains to methods for treating dyssomnias in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 One aspect of the present invention pertains to methods for treating insomnia in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

 One aspect of the present invention pertains to methods for treating parasomnias in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25 One aspect of the present invention pertains to methods for increasing slow wave sleep in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30 One aspect of the present invention pertains to methods for improving sleep consolidation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

 One aspect of the present invention pertains to methods for improving sleep maintenance in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating conditions associated with platelet aggregation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5 One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10 One aspect of the present invention pertains to methods for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 One aspect of the present invention pertains to methods for treating diabetic-related disorders in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20 One aspect of the present invention pertains to methods for treating progressive multifocal leukoencephalopathy in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for treating hypertension in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25 One aspect of the present invention pertains to methods for treating pain in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a sleep disorder.

30 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a dyssomnia.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of insomnia.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a parasomnia.

35 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for increasing slow wave sleep.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for improving sleep consolidation.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for improving sleep maintenance.

5 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient
10 ischemic attack, angina, stroke and atrial fibrillation.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a condition associated with platelet aggregation.

One aspect of the present invention pertains to use of compounds of the present
15 invention for the manufacture of a medicament for the reduction of the risk of blood clot formation in an angioplasty or coronary bypass surgery individual.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual.

20 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual suffering from atrial fibrillation.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of a diabetic-related disorder.

25 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of progressive multifocal leukoencephalopathy.

One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of hypertension.

30 One aspect of the present invention pertains to use of compounds of the present invention for the manufacture of a medicament for the treatment of pain.

One aspect of the present invention pertains to use of compounds of the present invention for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for
35 use in a method for the treatment of a 5-HT_{2A} mediated disorder in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a 5-HT_{2A} mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation in the human or animal body by therapy.

5 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a sleep disorder in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a dyssomnia in the human or animal body by therapy.

10 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of insomnia in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a parasomnia in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for increasing slow wave sleep in the human or animal body by therapy.

15 One aspect of the present invention pertains to compounds of the present invention for use in a method for improving sleep consolidation in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for improving sleep maintenance in the human or animal body by therapy.

20 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a condition associated with platelet aggregation in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual by therapy.

25 One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an individual by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method of reducing the risk of blood clot formation in an individual suffering from atrial fibrillation by therapy.

30 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of a diabetic-related disorder in the human or animal body by therapy.

35 One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of progressive multifocal leukoencephalopathy in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of hypertension in the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method for the treatment of pain in the human or animal body by therapy.

One aspect of the present invention pertains to processes for preparing a composition comprising admixing a compound of the present invention and a pharmaceutically acceptable carrier.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a general synthetic scheme for the preparation of compounds of the invention. A mono Boc-protected piperazine derivative is reacted with a halide, the Boc-group is removed and the piperazine is subsequently acylated with an indazole derivative. Alternatively, an unprotected piperazine derivative may be used.

Figure 2 shows two different methods used to modify the indazole moiety. The first is the palladium catalyzed conversion of an indazole halide to an indazole carbonitrile with zinc cyanide. The second is a Suzuki reaction of an indazole halide with a boronic acid to form an aryl or alkyl indazole.

Figure 3 shows three methods for the functionalization of the indazole nitrogens. Reaction of an indazole carboxylic acid with an alkyl or aryl sulfonyl chloride in the presence of base affords the sulfonamide. The indazole may also be *N*-alkylated by treatment with an alkyl halide in the presence of a base.

Figure 4 shows an alternative route for preparation of compounds of the present invention involving first a HOBt/EDAC mediated amide coupling of an aryl carboxylic acid derivative with a mono Boc-protected piperazine derivative. The resulting amide is reduced with borane, deprotected with HCl and coupled with an indazole carboxylic acid derivative in the presence of HATU.

Figure 5 shows a third general route to compounds of the invention. The first step is a HATU mediated amide coupling between a piperazine derivative and an indazole carboxylic acid. The intermediate is further derivatized by treatment with a halide in the presence of a base.

Figure 6 shows the efficacy of Compound 8 in the attenuation of DOI-induced hypolocomotion in rats.

Figure 7 shows the efficacy of Compound 17 in the attenuation of DOI-induced hypolocomotion in rats.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this
5 patent document.

The term “**agonists**” is intended to mean moieties that interact and activate the receptor, such as the 5-HT_{2A} serotonin receptor, and initiate a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

10 The term “**antagonists**” is intended to mean moieties that competitively bind to the receptor at the same site as agonists (for example, the endogenous ligand), but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. Antagonists do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

15 The term “**contact or contacting**” is intended to mean bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, “contacting” a 5-HT_{2A} serotonin receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a 5-HT_{2A} serotonin receptor, as well as, for example, introducing a compound of the invention into a sample
20 containing a cellular or more purified preparation containing a 5-HT_{2A} serotonin receptor.

The term “**in need of treatment**” and the term “**in need thereof**” when referring to treatment are used interchangeably to mean a judgment made by a caregiver (e.g. physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals), or a judgment made by a human individual that the individual
25 or an animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver’s expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or preventive manner; or compounds of the invention can
30 be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term “**individual**” is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

35 The term “**inverse agonists**” is intended to mean moieties that bind to the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP

binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

5 The term “**modulate or modulating**” is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term “**pharmaceutical composition**” is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates and hydrates of compounds of the present invention; whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of
10 ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term “**therapeutically effective amount**” is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical
15 doctor or other clinician or caregiver; or by a human individual, which includes one or more of the following:

- (1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease,
- 20 (2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology), and
- (3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder
25 in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

CHEMICAL GROUP, MOIETY OR RADICAL

The term “**C₁-C₆ acyl**” is intended to mean a C₁-C₆ alkyl radical attached to the carbon
30 of a carbonyl group wherein the definition of alkyl has the same definition as described herein; some examples include, but are not limited to, acetyl, propionyl, *n*-butanoyl, *iso*-butanoyl, pivaloyl, pentanoyl, hexanoyl and the like.

The term “**C₁-C₆ acyloxy**” is intended to mean an acyl radical attached to an oxygen atom wherein acyl has the same definition as described herein; some embodiments are when
35 acyloxy is C₁-C₅ acyloxy, some embodiments are when acyloxy is C₁-C₄ acyloxy. Some examples include, but are not limited to, acetyloxy, propionyloxy, *n*-butanoyloxy, *iso*-butanoyloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy and the like.

The term "**C₂-C₆ alkenyl**" is intended to mean a radical containing 2 to 6 carbons wherein at least one carbon-carbon double bond is present; some embodiments are 2 to 5 carbons, some embodiments are 2 to 4 carbons, some embodiments are 2 to 3 carbons, and some embodiments have 2 carbons. Both *E* and *Z* isomers are embraced by the term "**alkenyl**."

5 Furthermore, the term "**alkenyl**" includes di- and tri-alkenyls. Accordingly, if more than one double bond is present then the bonds may be all *E* or all *Z* or a mixture thereof. Examples of an alkenyl include vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2,4-hexadienyl and the like.

10 The term "**C₁-C₆ alkoxy**" is intended to mean a C₁-C₆ alkyl radical, as defined herein, attached directly to an oxygen atom, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, *sec*-butoxy and the like.

15 The term "**C₁-C₆ alkyl**" is intended to mean a straight or branched carbon radical containing 1 to 6 carbons, some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of an alkyl include, but not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, pentyl, *iso*-pentyl, *t*-pentyl, *neo*-pentyl, 1-methylbutyl [i.e., -CH(CH₃)CH₂CH₂CH₃], 2-methylbutyl [i.e., -CH₂CH(CH₃)CH₂CH₃], *n*-hexyl and the like.

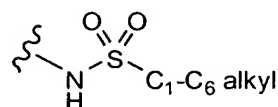
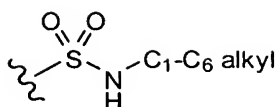
20 The term "**C₁-C₆ alkylcarboxamido**" or "**C₁-C₆ alkylcarboxamide**" is intended to mean a single C₁-C₆ alkyl group attached to either the carbon or the nitrogen of an amide group, wherein alkyl has the same definition as found herein. The C₁-C₆ alkylcarboxamido may be represented by the following:



25 Examples include, but are not limited to, *N*-methylcarboxamide, *N*-ethylcarboxamide, *N-n*-propylcarboxamide, *N*-isopropylcarboxamide, *N-n*-butylcarboxamide, *N-sec*-butylcarboxamide, *N-iso*-butylcarboxamide, *N-t*-butylcarboxamide and the like.

30 The term "**C₁-C₆ alkylsulfinyl**" is intended to mean a C₁-C₆ alkyl radical attached to the sulfur of a sulfoxide radical having the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *n*-butylsulfinyl, *sec*-butylsulfinyl, *iso*-butylsulfinyl, *t*-butylsulfinyl, and the like.

The term "**C₁-C₆ alkylsulfonamide**" is intended to mean the groups shown below:



wherein C₁-C₆ alkyl has the same definition as described herein.

The term “C₁-C₆ alkylsulfonyl” is intended to mean a C₁-C₆ alkyl radical attached to the sulfur of a sulfone radical having the formula: -S(O)₂- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, *iso*-butylsulfonyl, *t*-butylsulfonyl, and the like.

The term “C₁-C₆ alkylthio” is intended to mean a C₁-C₆ alkyl radical attached to a sulfur atom (i.e., -S-) wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfanyl (i.e., CH₃S-), ethylsulfanyl, *n*-propylsulfanyl, isopropylsulfanyl, *n*-butylsulfanyl, *sec*-butylsulfanyl, *iso*-butylsulfanyl, *t*-butylsulfanyl, and the like.

The term “C₁-C₆ alkylureyl” is intended to mean the group of the formula: -NC(O)N- wherein one or both of the nitrogens are substituted with the same or different C₁-C₆ alkyl group wherein alkyl has the same definition as described herein. Examples of an alkylureyl include, but are not limited to, CH₃NHC(O)NH-, NH₂C(O)NCH₃-, (CH₃)₂NC(O)NH-, (CH₃)₂NC(O)NCH₃-, CH₃CH₂NHC(O)NH-, CH₃CH₂NHC(O)NCH₃-, and the like.

The term “C₂-C₆ alkynyl” is intended to mean a radical containing 2 to 6 carbons and at least one carbon-carbon triple bond, some embodiments have 2 to 4 carbons, some embodiments have 2 to 3 carbons, and some embodiments have 2 carbons. Examples of an alkynyl include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, 5-hexyne and the like. The term “alkynyl” includes di- and tri-ynes.

The term “amino” is intended to mean the group -NH₂.

The term “C₁-C₆ alkylamino” is intended to mean one alkyl radical attached to a -NH- radical wherein the alkyl radical has the same meaning as described herein. Some examples include, but are not limited to, methylamino, ethylamino, *n*-propylamino, isopropylamino, *n*-butylamino, *sec*-butylamino, *iso*-butylamino, *t*-butylamino, and the like. Some embodiments are “C₁-C₂ alkylamino.”

The term “aryl” is intended to mean an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

The term “arylcarbonyl” is intended to mean an aryl radical attached to the carbon of a carbonyl group wherein the definition of aryl has the same definition as described herein; some examples include, but are not limited to, benzoyl and naphthylcarbonyl.

The term “**carbo-C₁-C₆-alkoxy**” is intended to mean a C₁-C₆ alkyl ester of a carboxylic acid, wherein the alkyl group is as defined herein. Examples include, but are not limited to, carbomethoxy [-C(=O)OCH₃], carboethoxy, carbopropoxy, carboisopropoxy, carbobutoxy, carbo-*sec*-butoxy, carbo-*iso*-butoxy, carbo-*t*-butoxy, carbo-*n*-pentoxy, carbo-*iso*-pentoxy, carbo-*t*-pentoxy, carbo-*neo*-pentoxy, carbo-*n*-hexyloxy, and the like.

The term “**carboxamide**” is intended to mean the group -CONH₂.

The term “**carboxy**” or “**carboxyl**” is intended to mean the group -CO₂H; also referred to as a carboxylic acid group.

The term “**cyano**” is intended to mean the group -CN.

The term “**C₃-C₇ cycloalkyl**” is intended to mean a saturated ring radical containing 3 to 7 carbons; some embodiments contain 3 to 6 carbons; some embodiments contain 3 to 5 carbons; some embodiments contain 5 to 7 carbons; some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term “**C₂-C₆ dialkylamino**” is intended to mean an amino substituted with two of the same or different C₁-C₃ alkyl radicals wherein alkyl radical has the same definition as described herein. Some examples include, but are not limited to, dimethylamino, methylethylamino, diethylamino, methylpropylamino, methylisopropylamino, ethylpropylamino, ethylisopropylamino, dipropylamino, propylisopropylamino and the like. Some embodiments are “**C₂-C₄ dialkylamino**.”

The term “**C₂-C₆ dialkylcarboxamido**” or “**C₂-C₆ dialkylcarboxamide**” is intended to mean two alkyl radicals, that are the same or different, attached to an amide group, wherein alkyl has the same definition as described herein. A C₂-C₆ dialkylcarboxamido may be represented by the following groups:



wherein C₁-C₃ has the same definition as described herein. Examples of a dialkylcarboxamide include, but are not limited to, *N,N*-dimethylcarboxamide, *N*-methyl-*N*-ethylcarboxamide, *N,N*-diethylcarboxamide, *N*-methyl-*N*-isopropylcarboxamide, and the like.

The term “**C₂-C₆ dialkylsulfonamide**” is intended to mean one of the following groups shown below:



wherein C₁-C₃ has the same definition as described herein, for example but not limited to, methyl, ethyl, *n*-propyl, isopropyl, and the like.

The term "**C₁-C₆ haloalkoxy**" is intended to mean a C₁-C₆ haloalkyl, as defined herein, which is directly attached to an oxygen atom. Examples include, but are not limited to, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy and the like.

The term "**C₁-C₆ haloalkyl**" is intended to mean an C₁-C₆ alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C₁-C₆ haloalkyl can be represented by the formula C_nL_{2n+1} wherein L is a halogen and "n" is 1, 2, 3, 4, 5 or 6; when more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term "**C₁-C₆ haloalkylsulfinyl**" is intended to mean a C₁-C₆ haloalkyl radical attached to the sulfur atom of a sulfoxide group having the formula: -S(O)- wherein the haloalkyl radical has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, 2,2-difluoroethylsulfinyl and the like.

The term "**C₁-C₆ haloalkylsulfonyl**" is intended to mean a C₁-C₆ haloalkyl radical attached to the sulfur atom of a sulfone group having the formula: -S(O)₂- wherein haloalkyl has the same definition as described herein. Examples include, but are not limited to, trifluoromethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, 2,2-difluoroethylsulfonyl and the like.

The term "**C₁-C₆ haloalkylthio**" is intended to mean a C₁-C₆ haloalkyl radical directly attached to a sulfur wherein the haloalkyl has the same meaning as described herein. Examples include, but are not limited to, trifluoromethylthio (i.e., CF₃S-, also referred to as trifluoromethylsulfanyl), 1,1-difluoroethylthio, 2,2,2-trifluoroethylthio and the like.

The term "**halogen**" or "**halo**" is intended to mean a fluoro, chloro, bromo or iodo group.

The term "**heteroaryl**" is intended to mean an aromatic ring system that may be a single ring, two fused rings or three fused rings wherein at least one ring carbon is replaced with a heteroatom selected from, for example, but not limited to, the group consisting of O, S and N wherein the N can be optionally substituted with H, C₁-C₄ acyl or C₁-C₄ alkyl. Examples of heteroaryl groups include, but are not limited to, pyrazolyl, indazolyl, pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinolinyl, benzoxazolyl, benzothiazolyl, 1H-benzimidazolyl, isoquinolinyl, quinazolinyl, quinoxalinyl and the like. In some embodiments, the heteroatom is selected from, for example, but not limited to, the group consisting of O, S and N, wherein N is substituted with H (i.e., NH), examples include, but are not limited to, pyrrolyl, indolyl, 1H-benzimidazol-2-yl, and the like.

The term “**heteroarylcarbonyl**” is intended to mean a heteroaryl radical attached to the carbon of a carbonyl group wherein the definition of heteroaryl has the same definition as described herein; some examples include, but are not limited to, pyrazoloyl and indazoloyl.

The term “**hydroxyl**” is intended to mean the group -OH.

5 The term “**nitro**” is intended to mean the group -NO₂.

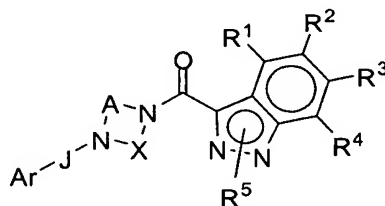
The term “**oxo**” is intended to mean the substituent =O, accordingly, as a result, when a carbon is substituted by an “oxo” group the new group resulting from the carbon and oxo together is a carbonyl group.

The term “**sulfonamide**” is intended to mean the group -SO₂NH₂.

10 The term “**thiol**” is intended to mean the group -SH.

COMPOUNDS OF THE INVENTION:

One aspect of the present invention pertains to certain compounds as shown in Formula (Ia):



(Ia)

15 or a pharmaceutically acceptable salt, hydrate or solvate thereof; wherein R¹, R², R³, R⁴, R⁵, Ar, A, X and J have the same definitions as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., R¹, R², R³, R⁴, R⁵, Ar, A, X and J) contained within the generic chemical formulae described herein (Ia, Ic and Ie) are specifically embraced by the present invention just as if they were explicitly disclosed, to the extent that such combinations embrace compounds that are stable (i.e., compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also specifically embraced by the present invention just as if each of such subcombination of chemical groups and subcombination of uses and medical indications were explicitly disclosed herein.

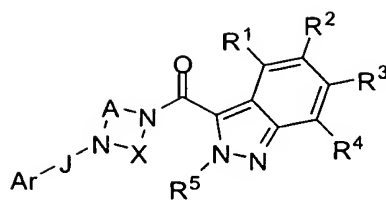
As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers, and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

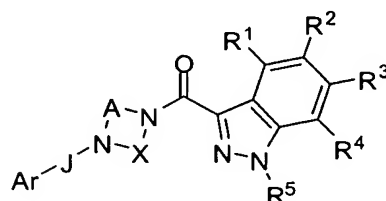
It is understood and appreciated that compounds of Formula (Ia) and formulae related therefrom may have one or more chiral centers, and therefore can exist as enantiomers and/or diastereomers. The invention is understood to extend to and embrace all such enantiomers, diastereomers and mixtures thereof, including but not limited to racemates. Accordingly, some embodiments of the present invention pertain to compounds of the present invention that are *R* enantiomers. Further, some embodiments of the present invention pertain to compounds of the present invention that are *S* enantiomers. In examples where more than one chiral center is present, then, some embodiments of the present invention include compounds that are *RS* or *SR* enantiomers. In further embodiments, compounds of the present invention are *RR* or *SS* enantiomers. It is understood that compounds of Formula (Ia) and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

Some embodiments of the present invention pertain to compounds of Formula (Ic):



(Ic)

Some embodiments of the present invention pertain to compounds of Formula (Ie):



(Ie)

In some embodiments each R^1 , R^2 , R^3 and R^4 is selected independently from the group consisting of H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, aryl, cyano, C_1 - C_6 haloalkoxy, halogen and heteroaryl; each optionally substituted with C_1 - C_6 alkyl.

In some embodiments each R^1 , R^2 , R^3 and R^4 is selected independently from the group consisting of H, methoxy, methyl, 2-methylphenyl, cyano, trifluoromethoxy, fluoro, chloro and bromo.

In some embodiments R^1 is H or C_1 - C_6 alkyl; R^2 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, aryl or halogen, and aryl is optionally substituted with C_1 - C_6 alkyl; R^3 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_1 - C_6 haloalkoxy or halogen; and R^4 is H or C_1 - C_6 alkoxy.

In some embodiments R^1 is H or methyl; R^2 is H, methoxy, methyl, 2-methyl-phenyl, fluoro, chloro or bromo; R^3 is H, methoxy, methyl, cyano, trifluoromethoxy, fluoro, chloro or bromo; and R^4 is H or methoxy.

In some embodiments R^5 is selected from the group consisting of H, C_1 - C_6 acyl, C_1 - C_6 alkyl, arylcarbonyl, arylsulfonyl, C_3 - C_7 cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens.

In some embodiments R^5 is selected from the group consisting of H, 1*H*-indazole-3-carbonyl, 4-fluorobenzoyl, methyl, ethyl, *n*-propyl, isopropyl, benzenesulfonyl and cyclopropyl.

In some embodiments A and X are each $-CH_2CH_2-$, and each optionally substituted with C_1 - C_3 alkyl.

In some embodiments A and X are each $-CH_2CH_2-$, and each optionally substituted with methyl.

In some embodiments A and X are each independently $-CH_2CH_2-$ or $-CH(CH_3)CH_2-$.

In some embodiments J is $-\text{CH}_2\text{CH}_2-$ optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo.

In some embodiments J is $-\text{CH}_2\text{CH}_2-$ optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of fluoro and oxo.

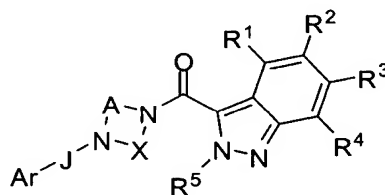
5 In some embodiments J is $-\text{CH}_2\text{CH}_2-$, $-\text{C}=\text{OCH}_2-$, $-\text{CHFCH}_2-$ or $-\text{CF}_2\text{CH}_2-$.

In some embodiments Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.

In some embodiments Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of fluoro and chloro.

10 In some embodiments Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.

Some embodiments of the present invention pertain to compounds of Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

15 R¹ is H or C₁-C₆ alkyl;

R² is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl or halogen, and aryl is optionally substituted with C₁-C₆ alkyl;

R³ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₁-C₆ haloalkoxy or halogen;

R⁴ is H or C₁-C₆ alkoxy;

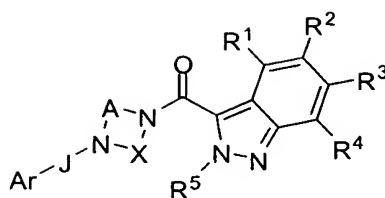
20 R⁵ is selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ alkyl, arylcarbonyl, arylsulfonyl, C₃-C₇ cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

A and X are each independently $-\text{CH}_2\text{CH}_2-$, and each optionally substituted with C₁-C₃ alkyl;

25 J is $-\text{CH}_2\text{CH}_2-$ optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo; and

Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.

Some embodiments of the present invention pertain to compounds of Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R¹ is H or methyl;

R² is H, methoxy, methyl, 2-methyl-phenyl, fluoro, chloro or bromo;

5 R³ is H, methoxy, methyl, cyano, trifluoromethoxy, fluoro, chloro or bromo;

R⁴ is H or methoxy;

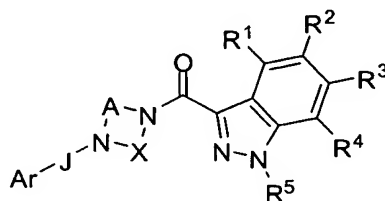
R⁵ is H, 1*H*-indazole-3-carbonyl, 4-fluorobenzoyl, methyl, ethyl, *n*-propyl, isopropyl, benzenesulfonyl or cyclopropyl;

A and X are each independently -CH₂CH₂- or -CH(CH₃)CH₂-;

10 J is -CH₂CH₂-, -C=OCH₂-, -CHFCH₂- or -CF₂CH₂-; and

Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.

Some embodiments of the present invention pertain to compounds of Formula (Ie):



(Ie)

15 or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R¹ is H or C₁-C₆ alkyl;

R² is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl or halogen, and aryl is optionally substituted with C₁-C₆ alkyl;

R³ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₁-C₆ haloalkoxy or halogen;

20 R⁴ is H or C₁-C₆ alkoxy;

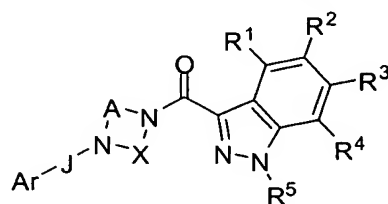
R⁵ is selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ alkyl, arylcarbonyl, arylsulfonyl, C₃-C₇ cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

25 A and X are each independently -CH₂CH₂-, and each optionally substituted with C₁-C₃ alkyl;

J is -CH₂CH₂- optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo; and

Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.

Some embodiments of the present invention pertain to compounds of Formula (Ie):



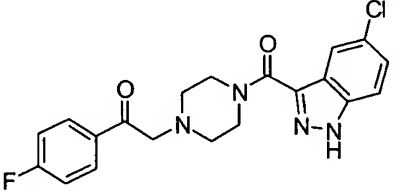
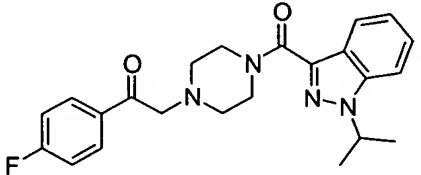
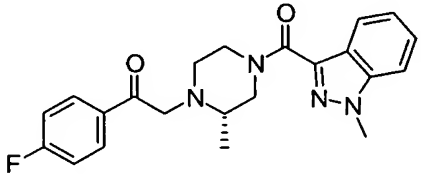
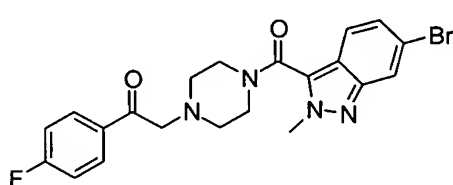
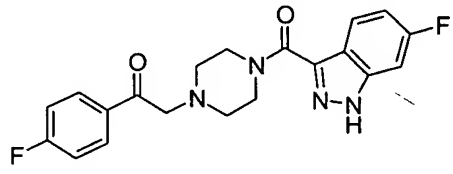
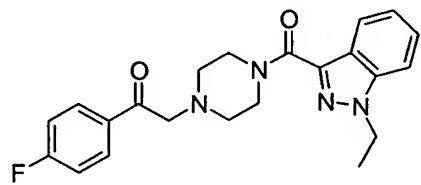
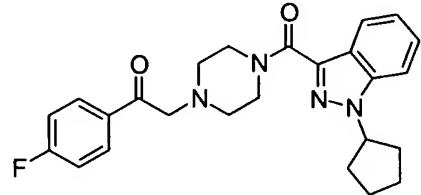
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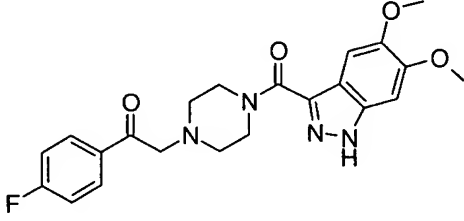
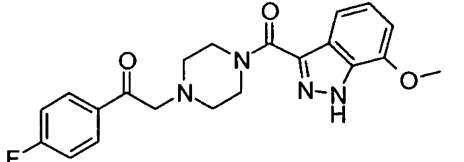
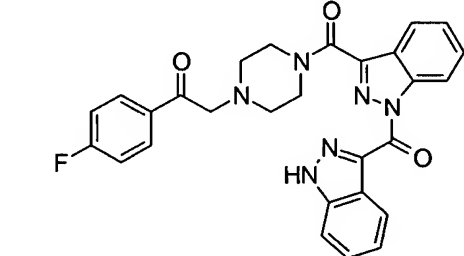
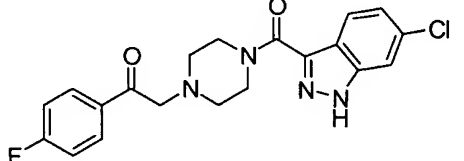
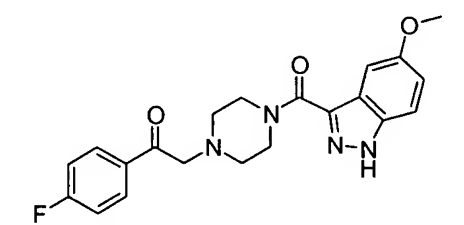
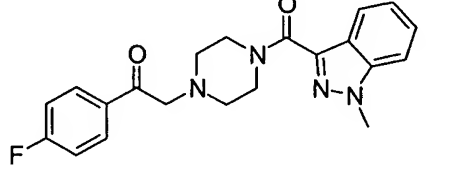
or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

- 5 R^1 is H or methyl;
 R^2 is H, methoxy, methyl, 2-methyl-phenyl, fluoro, chloro or bromo;
 R^3 is H, methoxy, methyl, cyano, trifluoromethoxy, fluoro, chloro or bromo;
 R^4 is H or methoxy;
 R^5 is H, 1*H*-indazole-3-carbonyl, 4-fluorobenzoyl, methyl, ethyl, *n*-propyl, isopropyl,
 10 benzenesulfonyl or cyclopropyl;
 A and X are each independently $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)\text{CH}_2-$;
 J is $-\text{CH}_2\text{CH}_2-$, $-\text{C}=\text{OCH}_2-$, $-\text{CHFCH}_2-$ or $-\text{CF}_2\text{CH}_2-$; and
 Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.
 15 Some embodiments of the present invention include every combination of one or more compounds selected from the following group shown in TABLE A.

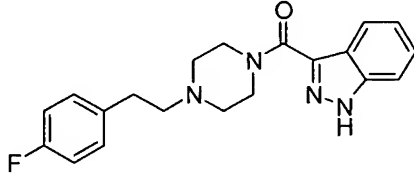
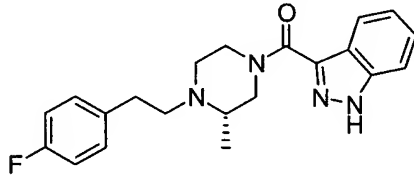
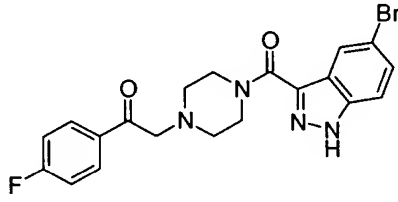
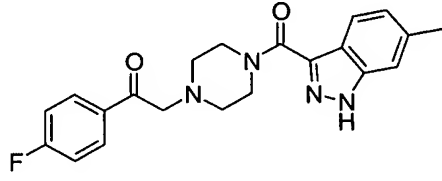
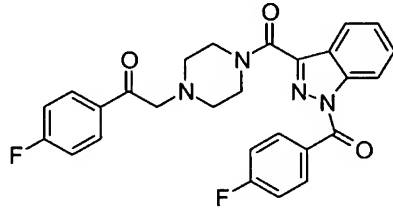
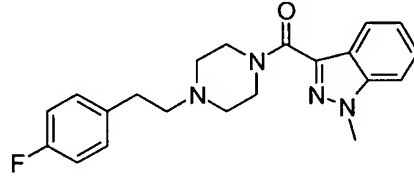
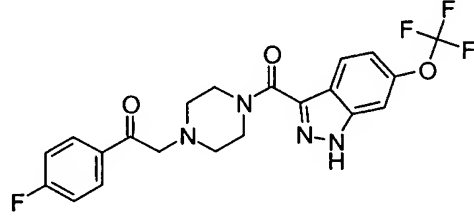
TABLE A

Cmpd No.	Chemical Structure	Chemical Name
1		1-(4-Fluorophenyl)-2-[(<i>S</i>)-4-(1 <i>H</i> -indazole-3-carbonyl)-2-methylpiperazin-1-yl]ethanone
2		3-{4-[2-(4-Fluorophenyl)-2-oxoethyl]piperazine-1-carbonyl}-1-methyl-1 <i>H</i> -indazole-6-carbonitrile

Cmpd No.	Chemical Structure	Chemical Name
3		2-[4-(5-Chloro-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
4		1-(4-Fluorophenyl)-2-[4-(1-isopropyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
5		1-(4-Fluorophenyl)-2-[(S)-2-methyl-4-(1-methyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
6		2-[4-(6-Bromo-2-methyl-2H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
7		2-[4-(6-Fluoro-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
8		2-[4-(1-Ethyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
9		2-[4-(1-Cyclopentyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone

Cmpd No.	Chemical Structure	Chemical Name
10		2-[4-(5,6-Dimethoxy-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
11		1-(4-Fluorophenyl)-2-[4-(7-methoxy-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
12		1-(4-Fluorophenyl)-2-{4-[1-(1H-indazole-3-carbonyl)-1H-indazole-3-carbonyl]-piperazin-1-yl}-ethanone
13		2-[4-(6-Chloro-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
14		1-(4-Fluorophenyl)-2-[4-(5-methoxy-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
15		1-(4-Fluorophenyl)-2-[4-(1-methyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone

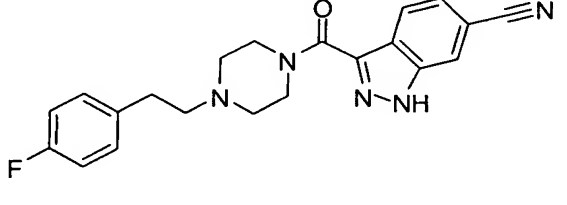
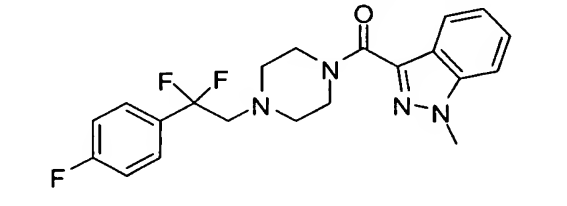
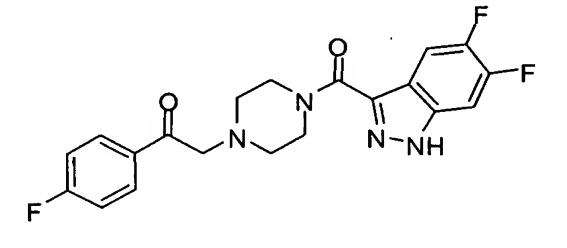
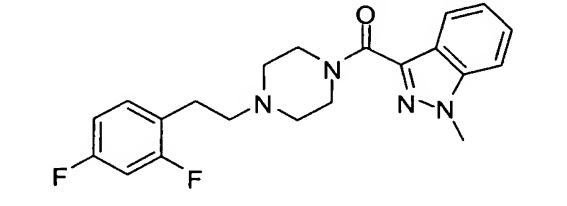
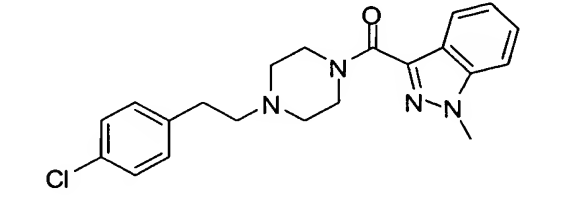
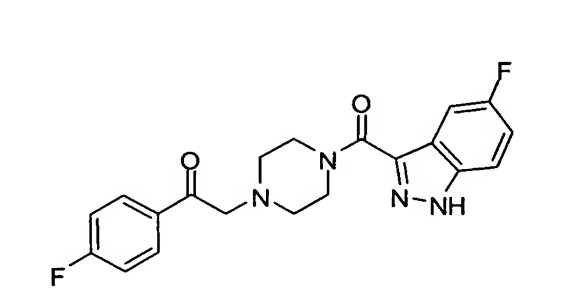
Cmpd No.	Chemical Structure	Chemical Name
16		{(S)-4-[2-(4-Fluorophenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1H-indazol-3-yl)-methanone
17		1-(4-Fluorophenyl)-2-[4-(6-methoxy-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
18		1-(4-Fluorophenyl)-2-[(S)-3-methyl-4-(1-methyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
19		1-(4-Fluorophenyl)-2-[4-(1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
20		{(R)-4-[2-(4-Fluorophenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1H-indazol-3-yl)-methanone
21		2-[4-(6-Bromo-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
22		2-[4-(6-Bromo-1-methyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone

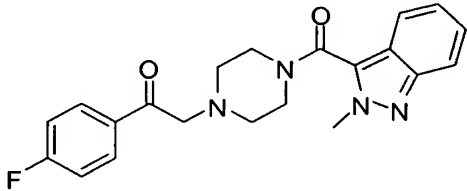
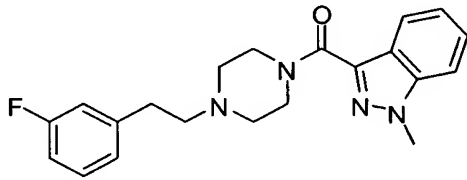
Cmpd No.	Chemical Structure	Chemical Name
23		{4-[2-(4-Fluorophenyl)-ethyl]-piperazin-1-yl}-(1 <i>H</i> -indazol-3-yl)-methanone
24		{(S)-4-[2-(4-Fluorophenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1 <i>H</i> -indazol-3-yl)-methanone
25		2-[4-(5-Bromo-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
26		1-(4-Fluorophenyl)-2-[4-(6-methyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
27		2-{4-[1-(4-Fluorobenzoyl)-1 <i>H</i> -indazole-3-carbonyl]-piperazin-1-yl}-1-(4-fluorophenyl)-ethanone
28		{4-[2-(4-Fluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
29		1-(4-Fluorophenyl)-2-[4-(6-trifluoromethoxy-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone

Cmpd No.	Chemical Structure	Chemical Name
30		1-(4-Fluorophenyl)-2-[4-(1-propyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
31		1-(4-Fluorophenyl)-2-[4-(6-o-tolyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
32		2-[4-(1-Benzenesulfonyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
33		{(R)-4-[2-(4-Fluorophenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1 <i>H</i> -indazol-3-yl)-methanone
34		1-(4-Fluorophenyl)-2-[4-(5-o-tolyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
35		3-{4-[2-(4-Fluorophenyl)-ethyl]-piperazine-1-carbonyl}-2-methyl-2 <i>H</i> -indazole-6-carbonitrile

Cmpd No.	Chemical Structure	Chemical Name
36		{4-[2-(3-Chlorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
37		1-(4-Fluorophenyl)-2-[4-(6-methoxy-1-methyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
38		{4-[2-(2-Fluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
39		1-(4-Chlorophenyl)-2-[4-(1-methyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
40		3-{4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1 <i>H</i> -indazole-6-carbonitrile
41		{4-[2-(2-Chlorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
42		3-{4-[2-(4-Fluorophenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1 <i>H</i> -indazole-6-carbonitrile

Cmpd No.	Chemical Structure	Chemical Name
43		(6-Bromo-1-methyl-1 <i>H</i> -indazol-3-yl)-{4-[2-(2,4-difluorophenyl)-ethyl]-piperazin-1-yl}-methanone
44		1-(4-Fluorophenyl)-2-[(<i>R</i>)-2-methyl-4-(1-methyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone
45		(6-Bromo-1-methyl-1 <i>H</i> -indazol-3-yl)-{4-[2-(4-fluorophenyl)-ethyl]-piperazin-1-yl}-methanone
46		(1-Ethyl-1 <i>H</i> -indazol-3-yl)-{4-[2-(4-fluorophenyl)-ethyl]-piperazin-1-yl}-methanone
47		{4-[2-Fluoro-2-(4-fluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
48		2-[4-(5,6-Dichloro-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
49		1-(4-Fluorophenyl)-2-[4-(5-methyl-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-ethanone

Cmpd No.	Chemical Structure	Chemical Name
50		3-{4-[2-(4-Fluorophenyl)-ethyl]-piperazine-1-carbonyl}-1 <i>H</i> -indazole-6-carbonitrile
51		{4-[2,2-Difluoro-2-(4-fluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
52		2-[4-(5,6-Difluoro-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone
53		{4-[2-(2,4-Difluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
54		{4-[2-(4-Chlorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1 <i>H</i> -indazol-3-yl)-methanone
55		2-[4-(5-Fluoro-1 <i>H</i> -indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluorophenyl)-ethanone

Cmpd No.	Chemical Structure	Chemical Name
56		1-(4-Fluorophenyl)-2-[4-(2-methyl-2H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone
57		{4-[2-(3-Fluorophenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1H-indazol-3-yl)-methanone

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in TABLE A including diastereomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates, and particularly hydrates, thereof.

The compounds of the Formula (Ia) of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3rd Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

It is understood that the present invention embraces each diastereomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers (such as, chiral HPLC, recrystallization of diastereomeric mixtures, and the like) or selective synthesis (such as, enantiomeric selective syntheses, and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

INDICATIONS AND METHODS OF TREATMENT

In addition to the foregoing beneficial uses for the modulators of 5-HT_{2A} serotonin receptor activity disclosed herein, the compounds disclosed herein are believed to be useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

1. Sleep disorders

It is reported in the National Sleep Foundation's 2002 Sleep In America Poll, more than one-half of the adults surveyed (58%) report having experienced one or more symptoms of insomnia at least a few nights a week in the past year. Additionally, about three in ten (35%) say they have experienced insomnia-like symptoms every night or almost every night.

5 The normal sleep cycle and sleep architecture can be disrupted by a variety of organic causes as well as environmental influences. According to the International Classification of Sleep Disorders, there are over 80 recognized sleep disorders. Of these, compounds of the present invention are effective, for example, in any one or more of the following sleep disorders (ICSD – International Classification of Sleep Disorders: Diagnostic and Coding Manual. *Diagnostic*
10 *Classification Steering Committee*, American Sleep Disorders Association, 1990):

A. DYSSOMNIAS

a. Intrinsic Sleep Disorders:

Psychophysiological insomnia, sleep state misperception, idiopathic insomnia, obstructive sleep apnea syndrome, central sleep apnea syndrome, central alveolar hypoventilation syndrome,
15 periodic limb movement disorder, restless leg syndrome and intrinsic sleep disorder NOS (not otherwise specified).

b. Extrinsic Sleep Disorders:

Inadequate sleep hygiene, environmental sleep disorder, altitude insomnia, adjustment sleep disorder, insufficient sleep syndrome, limit-setting sleep disorder, sleep onset association
20 disorder, nocturnal eating (drinking) syndrome, hypnotic-dependent sleep disorder, stimulant-dependent sleep disorder, alcohol-dependent sleep disorder, toxin-induced sleep disorder and extrinsic sleep disorder NOS.

c. Circadian Rhythm Sleep Disorders:

Time zone change (jet lag) syndrome, shift work sleep disorder, irregular sleep-wake
25 pattern, delayed sleep phase syndrome, advanced sleep phase syndrome, non-24-hour sleep-wake disorder and circadian rhythm sleep disorder NOS.

B. PARASOMNIAS

a. Arousal Disorders:

Confusional arousals, sleepwalking and sleep terrors.

30 b. Sleep-Wake Transition Disorders:

Rhythmic movement disorder, sleep starts, sleep talking and nocturnal leg cramps.

**C. SLEEP DISORDERS ASSOCIATED WITH MEDICAL/PSYCHIATRIC
DISORDERS**

a. Associated with Mental Disorders:

35 Psychoses, mood disorders, anxiety disorders, panic disorders and alcoholism.

b. Associated with Neurological Disorders:

Cerebral degenerative disorders, dementia, Parkinsonism, fatal familial insomnia, sleep-related epilepsy, electrical status epilepticus of sleep and sleep-related headaches.

c. Associated with Other Medical Disorders:

5 Sleeping sickness, nocturnal cardiac ischemia, chronic obstructive pulmonary disease, sleep-related asthma, sleep-related gastroesophageal reflux, peptic ulcer disease, fibrositis syndrome, osteoarthritis, rheumatoid arthritis, fibromyalgia and post-surgical.

The effects of sleep deprivation are more than excessive daytime sleepiness. Chronic insomniacs report elevated levels of stress, anxiety, depression and medical illnesses (National Institutes of Health, National Heart, Lung, and Blood Institute, *Insomnia Facts Sheet*, Oct. 1995).
10 Preliminary evidence suggests that having a sleep disorder that causes significant loss of sleep may contribute to increased susceptibility to infections due to immunosuppression, cardiovascular complications such as hypertension, cardiac arrhythmias, stroke, and myocardial infarction, compromised glucose tolerance, increased obesity and metabolic syndrome. Compounds of the present invention are useful to prevent or alleviate these complications by improving sleep quality.

15 The most common class of medications for the majority of sleep disorders are the benzodiazepines, but the adverse effect profile of benzodiazepines include daytime sedation, diminished motor coordination, and cognitive impairments. Furthermore, the National Institutes of Health Consensus conference on Sleeping Pills and Insomnia in 1984 have developed guidelines discouraging the use of such sedative-hypnotics beyond 4-6 weeks because of concerns raised over
20 drug misuse, dependency, withdrawal and rebound insomnia. Therefore, it is desirable to have a pharmacological agent for the treatment of insomnia, which is more effective and/or has fewer side effects than those currently used. In addition, benzodiazepines are used to induce sleep, but have little to no effect on the maintenance of sleep, sleep consolidation or slow wave sleep. Therefore, sleep maintenance disorders are not currently well treated.

25 Clinical studies with agents of a similar mechanism of action to compounds of the present invention have demonstrated significant improvements on objective and subjective sleep parameters in normal, healthy volunteers as well as patients with sleep disorders and mood disorders [Sharpley A. L., *et al.* Slow Wave Sleep in Humans: Role of 5-HT_{2A} and 5HT_{2C} Receptors. *Neuropharmacology*, 1994, Vol. 33(3/4):467-71; Winokur A., *et al.* Acute Effects of
30 Mirtazapine on Sleep Continuity and Sleep Architecture in Depressed Patients: A Pilot Study. *Soc. of Biol. Psych.*, 2000, Vol. 48:75-78; and Landolt H. P., *et al.* Serotonin-2 Receptors and Human Sleep: Effect of Selective Antagonist on EEG Power Spectra. *Neuropsychopharmacology*, 1999, Vol. 21(3):455-66].

Some sleep disorders are sometimes found in conjunction with other conditions and
35 accordingly those conditions are treatable by compounds of Formula (Ia). For example, but not limited to, patients suffering from mood disorders typically suffer from a sleep disorder that can be treatable by compounds of Formula (Ia). Having one pharmacological agent which treats two or

more existing or potential conditions, as does the present invention, is more cost effective, leads to better compliance and has fewer side effects than taking two or more agents.

It is an object of the present invention to provide a therapeutic agent for the use in treating sleep disorders. It is another object of the present invention to provide one pharmaceutical agent, which may be useful in treating two or more conditions wherein one of the conditions is a sleep disorder. Compounds of the present invention described herein may be used alone or in combination with a mild sleep inducer (i.e. antihistamine).

Sleep Architecture:

Sleep comprises two physiological states: Non rapid eye movement (NREM) and rapid eye movement (REM) sleep. NREM sleep consists of four stages, each of which is characterized by progressively slower brain wave patterns, with the slower patterns indicating deeper sleep. Delta sleep, stages 3 and 4 of NREM sleep, is the deepest and most refreshing type of sleep. Many patients with sleep disorders are unable to adequately achieve the restorative sleep of stages 3 and 4. In clinical terms, patients' sleep patterns are described as fragmented, meaning the patient spends a lot of time alternating between stages 1 and 2 (semi-wakefulness) and being awake and very little time in deep sleep. As used herein, the term "fragmented sleep architecture" means an individual, such as a sleep disorder patient, spends the majority of their sleep time in NREM sleep stages 1 and 2, lighter periods of sleep from which the individual can be easily aroused to a waking state by limited external stimuli. As a result, the individual cycles through frequent bouts of light sleep interrupted by frequent awakenings throughout the sleep period. Many sleep disorders are characterized by a fragmented sleep architecture. For example, many elderly patients with sleep complaints have difficulty achieving long bouts of deep, refreshing sleep (NREM stages 3 and 4) and instead spend the majority of their sleep time in NREM sleep stages 1 and 2.

In contrast to fragmented sleep architecture, as used herein the term "sleep consolidation" means a state in which the number of NREM sleep bouts, particularly Stages 3 and 4, and the length of those sleep bouts are increased, while the number and length of waking bouts are decreased. In essence, the architecture of the sleep disorder patient is consolidated to a sleeping state with increased periods of sleep and fewer awakenings during the night and more time is spent in slow wave sleep (stages 3 and 4) with fewer oscillation stage 1 and 2 sleep. Compounds of the present invention can be effective in consolidating sleep patterns so that the patient with previously fragmented sleep can now achieve restorative, delta-wave sleep for longer, more consistent periods of time.

As sleep moves from stage 1 into later stages, heart rate and blood pressure drop, metabolic rate and glucose consumption fall, and muscles relax. In normal sleep architecture, NREM sleep makes up about 75% of total sleep time; stage 1 accounting for 5-10% of total sleep time, stage 2 for about 45-50%, stage 3 approximately 12%, and stage 4 13-15%. About 90

minutes after sleep onset, NREM sleep gives way to the first REM sleep episode of the night.

REM makes up approximately 25% of total sleep time. In contrast to NREM sleep, REM sleep is characterized by high pulse, respiration, and blood pressure, as well as other physiological patterns similar to those seen in the active waking stage. Hence, REM sleep is also known as “paradoxical

sleep.” Sleep onset occurs during NREM sleep and takes 10-20 minutes in healthy young adults.

The four stages of NREM sleep together with a REM phase form one complete sleep cycle that is repeated throughout the duration of sleep, usually four or five times. The cyclical nature of sleep is regular and reliable: a REM period occurs about every 90 minutes during the night. However, the first REM period tends to be the shortest, often lasting less than 10 minutes, whereas the later REM periods may last up to 40 minutes. With aging, the time between retiring and sleep onset increases and the total amount of night-time sleep decreases because of changes in sleep architecture that impair sleep maintenance as well as sleep quality. Both NREM (particularly stages 3 and 4) and REM sleep are reduced. However, stage 1 NREM sleep, which is the lightest sleep, increases with age.

As used herein, the term “delta power” means a measure of the duration of EEG activity in the 0.5 to 3.5 Hz range during NREM sleep and is thought to be a measure of deeper, more refreshing sleep. Delta power is hypothesized to be a measure of a theoretical process called Process S and is thought to be inversely related to the amount of sleep an individual experiences during a given sleep period. Sleep is controlled by homeostatic mechanisms; therefore, the less one sleeps the greater the drive to sleep. It is believed that Process S builds throughout the wake period and is discharged most efficiently during delta power sleep. Delta power is a measure of the magnitude of Process S prior to the sleep period. The longer one stays awake, the greater Process S or drive to sleep and thus the greater the delta power during NREM sleep. However, individuals with sleep disorders have difficulty achieving and maintaining delta wave sleep, and thus have a large build-up of Process S with limited ability to discharge this buildup during sleep. 5-HT_{2A} agonists tested preclinically and clinically mimic the effect of sleep deprivation on delta power, suggesting that subjects with sleep disorders treated with a 5-HT_{2A} inverse agonist or antagonist will be able to achieve deeper sleep that is more refreshing. These same effects have not been observed with currently marketed pharmacotherapies. In addition, currently marketed pharmacotherapies for sleep have side effects such as hangover effects or addiction that are associated with the GABA receptor. 5-HT_{2A} inverse agonists do not target the GABA receptor and so these side effects are not a concern.

Subjective and objective determinations of sleep disorders:

There are a number of ways to determine whether the onset, duration or quality of sleep (e.g. non-restorative or restorative sleep) is impaired or improved. One method is a subjective determination of the patient, e.g., do they feel drowsy or rested upon waking. Other methods

involve the observation of the patient by another during sleep, e.g., how long it takes the patient to fall asleep, how many times the patient wakes up during the night, how restless is the patient during sleep, etc. Another method is to measure the stages of sleep objectively using polysomnography.

5 Polysomnography is the monitoring of multiple electrophysiological parameters during sleep and generally includes measurement of EEG activity, electroculographic activity and electromyographic activity, as well as other measurements. These results, along with observations, can measure not only sleep latency (the amount of time required to fall asleep), but also sleep continuity (overall balance of sleep and wakefulness) and sleep consolidation (percent of sleeping
10 time spent in delta-wave or restorative sleep) which may be an indication of the quality of sleep.

There are five distinct sleep stages, which can be measured by polysomnography: rapid eye movement (REM) sleep and four stages of non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4). Stage 1 NREM sleep is a transition from wakefulness to sleep and occupies about 5% of time spent asleep in healthy adults. Stage 2 NREM sleep, which is characterized by specific
15 EEG waveforms (sleep spindles and K complexes), occupies about 50% of time spent asleep. Stages 3 and 4 NREM sleep (also known collectively as slow-wave sleep and delta-wave sleep) are the deepest levels of sleep and occupy about 10-20% of sleep time. REM sleep, during which the majority of vivid dreams occur, occupies about 20-25% of total sleep.

These sleep stages have a characteristic temporal organization across the night. NREM
20 stages 3 and 4 tend to occur in the first one-third to one-half of the night and increase in duration in response to sleep deprivation. REM sleep occurs cyclically through the night. Alternating with NREM sleep about every 80-100 minutes. REM sleep periods increase in duration toward the morning. Human sleep also varies characteristically across the life span. After relative stability with large amounts of slow-wave sleep in childhood and early adolescence, sleep continuity and
25 depth deteriorate across the adult age range. This deterioration is reflected by increased wakefulness and stage 1 sleep and decreased stages 3 and 4 sleep.

In addition, the compounds of the invention can be useful for the treatment of the sleep disorders characterized by excessive daytime sleepiness such as narcolepsy. Inverse agonists at the serotonin 5-HT_{2A} receptor improve the quality of sleep at nighttime which can decrease excessive
30 daytime sleepiness.

Accordingly, another aspect of the present invention relates to the therapeutic use of compounds of the present invention for the treatment of sleep disorders. Compounds of the present invention are potent inverse agonists at the serotonin 5-HT_{2A} receptor and can be effective in the treatment of sleep disorders by promoting one or more of the following: reducing the sleep
35 onset latency period (measure of sleep induction), reducing the number of nighttime awakenings, and prolonging the amount of time in delta-wave sleep (measure of sleep quality enhancement and sleep consolidation) without effecting REM sleep. In addition, compounds of the present

invention can be effective either as a monotherapy or in combination with sleep inducing agents, for example but not limited to, antihistamines.

Pharmacodynamic effects of the selective 5-HT_{2A} inverse agonist APD125 in healthy

5 **adults:**

APD125, a potent and selective 5-HT_{2A} serotonin receptor inverse agonist is a member of the genus disclosed in the European Patent EP1558582. In Phase 1 trials, APD125 showed vigilance-lowering effects on waking EEG, with maximal effects at 40-80 mg; peak effects were observed at 2-4 h after dosing. In the afternoon nap model of insomnia in normal
10 volunteers, APD125 increased slow wave sleep and associated parameters in a dose-dependent manner, primarily during the early part of sleep. These effects occurred at the expense of REM sleep. Sleep onset latency was not decreased by APD125. In the afternoon nap model, APD125 decreased microarousals, the number of sleep stage shifts, and number of awakenings after sleep onset.

15 In conclusion, APD125, a 5-HT_{2A} serotonin receptor inverse agonist, improved parameters of sleep consolidation and maintenance in humans. Thus, compounds of the invention, also highly selective 5-HT_{2A} serotonin receptor inverse agonists, will offer similar improvements in sleep parameters.

20 **2. Antiplatelet therapies (Conditions related to platelet aggregation):**

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (e.g., coronary thrombosis).

25 In a myocardial infarction (heart attack), the heart muscle does not receive enough oxygen-rich blood because of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 minutes), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot.
30 Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

35 Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter-based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedures.

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from
5 elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial
10 fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

5-HT_{2A} serotonin receptors are expressed on smooth muscle of blood vessels and 5-HT
15 secreted by activated platelets causes vasoconstriction as well as activation of additional platelets during clotting. There is evidence that a 5-HT_{2A} inverse agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see Satimura, K., *et al.*, *Clin. Cardiol.* 2002 Jan 25 (1):28-32; and Wilson, H. C. *et al.*, *Thromb. Haemost.* 1991 Sep 2;66(3):355-60).

5-HT_{2A} inverse agonists can be used to treat, for example, claudication or peripheral
20 artery disease as well as cardiovascular complications (see *Br. Med. J.* 298: 424-430, 1989), arterial thrombosis (see, Pawlak, D. *et al. Thrombosis Research* 90: 259-270, 1998), atherosclerosis (see, Hayashi, T. *et al. Atherosclerosis* 168: 23-31, 2003), vasoconstriction caused by serotonin (see, Fujiwara, T. and Chiba, S. *Journal of Cardiovascular Pharmacology* 26: 503-510, 1995), restenosis of arteries following angioplasty or stent placement (see, Fujita, M. *et al. Am. Heart J.* 145:e16, 2003). 5-HT_{2A} inverse antagonists can also be used alone or in
25 combination with thrombolytic therapy, for example, tissue plasminogen activator (tPA) (see, Yamashita, T. *et al. Haemostasis* 30:321-332, 2000), to provide cardioprotection following MI or postischemic myocardial dysfunction (see, Muto, T. *et al. Mol. Cell. Biochem.* 272: 119-132, 2005) or protection from ischemic injury during percutaneous coronary intervention (see,
30 Horibe, E. *Circulation Research* 68: 68-72, 2004), and the like, including complications resulting therefrom.

5-HT_{2A} inverse antagonists can increase circulating adiponectin in patients, suggesting that they would also be useful in protecting patients against indications that are linked to adiponectin, for example, myocardial ischemia reperfusion injury and atherosclerosis (see
35 Nomura *et al. Blood Coagulation and Fibrinolysis* 2005, 16, 423-428).

The 5-HT_{2A} inverse agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive

products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from atrial fibrillation, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein at a time where such risk exists.

3. Asthma

5-HT (5-hydroxytryptamine) has been linked to the pathophysiology of acute asthma (see Cazzola, M. and Matera, M. G., *Trends Pharmacol. Sci.* 21: 201-202, 2000; and De Bie, J. J. *et al.*, *British J. Pharm.*, 1998, 124, 857-864). The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

4. Agitation

Agitation is a well-recognized behavioral syndrome with a range of symptoms, including hostility, extreme excitement, poor impulse control, tension and uncooperativeness (See Cohen-Mansfield, J. and Billig, N. (1986), *Agitated Behaviors in the Elderly. I. A Conceptual Review. J. Am. Geriatr. Soc.* 34(10): 711-721).

Agitation is a common occurrence in the elderly and is often associated with dementia such as those caused by Alzheimer's disease, Lewy Body, Parkinson's, and Huntington's, which are degenerative diseases of the nervous system. Diseases that affect blood vessels, such as stroke, or multi-infarct dementia, which is caused by multiple strokes in the brain can also induce agitation. Alzheimer's disease accounts for approximately 50 to 70% of all dementias (See Koss, E. *et al.*, (1997), *Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. The Alzheimer's Disease Cooperative Study. Alzheimer Dis. Assoc. Disord.* 11(suppl 2):S45-S50).

An estimated 5% of people aged 65 and older and up to 20% of those aged 80 and older are affected by dementia; of these sufferers, nearly half exhibit behavioral disturbances, such as agitation, wandering and violent outbursts.

5 Agitated behaviors can also be manifested in cognitively intact elderly people and by those with psychiatric disorders other than dementia.

Agitation is often treated with antipsychotic medications such as haloperidol in nursing home and other assisted care settings. There is emerging evidence that agents acting at the 5-HT_{2A} serotonin receptors in the brain have the effects of reducing agitation in patients, including Alzheimer's dementia (See Katz, I. R. *et al. J. Clin. Psychiatry* 1999 Feb., 60(2):107-115; and
10 Street, J. S. *et al. Arch. Gen. Psychiatry* 2000 Oct., 57(10):968-976).

The compounds of the invention disclosed herein are useful for treating agitation and symptoms thereof. Thus, in some embodiments, the present invention provides methods for treating agitation in a patient in need of such treatment comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments, the
15 agitation is due to a psychiatric disorder other than dementia. In some embodiments, the present invention provides methods for treatment of agitation or a symptom thereof in a patient suffering from dementia comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein. In some embodiments of such methods, the dementia is due to a degenerative disease of the nervous system, for example and without limitation, Alzheimer's
20 disease, Lewy Body, Parkinson's disease, and Huntington's disease, or dementia due to diseases that affect blood vessels, including, without limitation, stroke and multi-infarct dementia. In some embodiments, methods are provided for treating agitation or a symptom thereof in a patient in need of such treatment, where the patient is a cognitively intact elderly patient, comprising administering to the patient a composition comprising a 5-HT_{2A} inverse agonist disclosed herein.

25

5. Add-on therapy to haloperidol in the treatment of schizophrenia and other disorders

Schizophrenia is a psychopathic disorder of unknown origin, which usually appears for the first time in early adulthood and is marked by a number of characteristics, psychotic symptoms,
30 progression, phasic development and deterioration in social behavior and professional capability in the region below the highest level ever attained. Characteristic psychotic symptoms are disorders of thought content (multiple, fragmentary, incoherent, implausible or simply delusional contents or ideas of persecution) and of mentality (loss of association, flight of imagination, incoherence up to incomprehensibility), as well as disorders of perceptibility (hallucinations), of emotions
35 (superficial or inadequate emotions), of self-perception, of intentions and impulses, of interhuman relationships, and finally psychomotoric disorders (such as catatonia). Other symptoms are also associated with this disorder: see, *American Statistical and Diagnostic Handbook*.

Haloperidol (Haldol) is a potent dopamine D₂ receptor antagonist. It is widely prescribed for acute schizophrenic symptoms, and is very effective for the positive symptoms of schizophrenia. However, Haldol is not effective for the negative symptoms of schizophrenia and may actually induce negative symptoms as well as cognitive dysfunction. In accordance with some methods of the invention, adding a 5-HT_{2A} inverse agonist concomitantly with Haldol will provide benefits including the ability to use a lower dose of Haldol without losing its effects on positive symptoms, while reducing or eliminating its inductive effects on negative symptoms, and prolonging relapse to the patient's next schizophrenic event.

Haloperidol is used for treatment of a variety of behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS). Further uses include in the treatment of infantile autism, Huntington's chorea, and nausea and vomiting from chemotherapy and chemotherapeutic antibodies. Administration of 5-HT_{2A} inverse agonists disclosed herein with haloperidol will also provide benefits in these indications.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating a behavioral disorder, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorders, psychosis (organic and NOS), psychotic disorder, psychosis, schizophrenia (acute, chronic and NOS) comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein.

In some embodiments, the present invention provides methods for treating infantile autism, Huntington's chorea, or nausea and vomiting from chemotherapy or chemotherapeutic antibodies comprising administering to the patient haloperidol and a 5-HT_{2A} inverse agonist disclosed herein.

In further embodiments, the present invention provides methods for treating schizophrenia in a patient in need of the treatment comprising administering to the patient a dopamine D₂ receptor antagonist and a 5-HT_{2A} inverse agonist disclosed herein. Preferably, the dopamine D₂ receptor antagonist is haloperidol.

The administration of the dopamine D₂ receptor antagonist can be concomitant with administration of the 5-HT_{2A} inverse agonist, or they can be administered at different times. Those of skill in the art will easily be able to determine appropriate dosing regimes for the most efficacious reduction or elimination of deleterious haloperidol effects. In some embodiments, haloperidol and the 5-HT_{2A} inverse agonist are administered in a single dosage form, and in other

The present invention further provides methods of alleviating negative symptoms of schizophrenia induced by the administration of haloperidol to a patient suffering from schizophrenia, comprising administering to the patient a 5-HT_{2A} inverse agonist as disclosed herein.

6. Diabetic-related pathologies

Although hyperglycemia is the major cause for the pathogenesis of diabetic complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), increased plasma serotonin concentration in diabetic patients has also been implicated to play a role in disease progression (Pietraszek, M. H. *et al. Thrombosis Res.* 1992, 66(6), 765-74; and Andrzejewska-Buczko J., *et al. Klin. Oczna.* 1996; 98(2), 101-4). Serotonin is believed to play a role in vasospasm and increased platelet aggregability. Improving microvascular blood flow is beneficial to diabetic complications.

A recent study by Cameron and Cotter in *Naunyn Schmiedebergs Arch. Pharmacol.* 2003 Jun; 367(6):607-14, used a 5-HT_{2A} antagonist experimental drug AT-1015, and other non-specific 5-HT_{2A} antagonists including ritanserin and sarpogrelate. These studies found that all three drugs were able to produce a marked correction (82.6-99.7%) of a 19.8% sciatic motor conduction deficit in diabetic rats. Similarly, 44.7% and 14.9% reductions in sciatic endoneurial blood flow and saphenous sensory conduction velocity were completely reversed.

In a separate patient study, sarpogrelate was evaluated for the prevention of the development or progression of diabetic nephropathy (Takahashi, T., *et al. Diabetes. Res. Clin. Pract.* 2002 Nov; 58(2):123-9). In the trial of 24 months of treatment, sarpogrelate significantly reduced urinary albumin excretion level.

7. Glaucoma

Topical ocular administration of 5-HT₂ receptor antagonists result in a decrease in intra ocular pressure (IOP) in monkeys (Chang *et al. J. Ocul. Pharmacol.* 1:137-147 (1985)) and humans (Mastropasqua *et al. Acta. Ophthalmol. Scand. Suppl.* 224:24-25 (1997)) indicating utility for similar compounds such as 5-HT_{2A} inverse agonists in the treatment of ocular hypertension associated with glaucoma. The 5-HT₂ receptor antagonist ketanserin

(Mastropasqua *supra*) and sarpogrelate (Takenaka *et al. Investig. Ophthalmol. Vis. Sci.* 36:S734 (1995)) have been shown to significantly lower IOP in glaucoma patients.

8. Progressive multifocal leukoencephalopathy

5 Progressive multifocal leukoencephalopathy (PML) is a lethal demyelinating disease caused by an opportunistic viral infection of oligodendrocytes in immunocompromised patients. The causative agent is JC virus, a ubiquitous papovavirus that infects the majority of the population before adulthood and establishes a latent infection in the kidney. In immunocompromised hosts, the virus can reactivate and productively infect oligodendrocytes. This previously rare condition, 10 until 1984 reported primarily in persons with underlying lymphoproliferative disorders, is now more common because it occurs in 4% of patients with AIDS. Patients usually present with relentlessly progressive focal neurologic defects, such as hemiparesis or visual field deficits, or with alterations in mental status. On brain MRI, one or more white matter lesions are present; they are hyperintense on T2-weighted images and hypointense on T1-weighted images. There is no 15 mass effect, and contrast enhancement is rare. Diagnosis can be confirmed by brain biopsy, with demonstration of virus by *in situ* hybridization or immunocytochemistry. Polymerase chain reaction amplification of JC virus sequences from the CSF can confirm diagnosis without the need for biopsy [Antinori *et al. Neurology* (1997) 48:687-694; Berger and Major *Seminars in Neurology* (1999) 19:193-200; and Portegies *et al. Eur. J. Neurol.* (2004) 11:297-304]. Currently, there is 20 no effective therapy. Survival after diagnosis is about 3 to 5 months in AIDS patients.

JC virus enters cells by receptor-mediated clathrin-dependent endocytosis. Binding of JC virus to human glial cells (e.g., oligodendrocytes) induces an intracellular signal that is critical for entry and infection by a ligand-inducible clathrin-dependent mechanism [Querbes *et al. J. Virology* (2004) 78:250-256]. Recently, 5-HT_{2A} was shown to be the receptor on human glial cells 25 mediating infectious entry of JC virus by clathrin-dependent endocytosis [Elphick *et al. Science* (2004) 306:1380-1383]. 5-HT_{2A} antagonists, including ketanserin and ritanserin, inhibited JC virus infection of human glial cells. Ketanserin and ritanserin have inverse agonist activity at 5-HT_{2A}.

5-HT_{2A} antagonists including inverse agonists have been contemplated to be useful in 30 the treatment of PML [Elphick *et al. Science* (2004) 306:1380-1383]. Prophylactic treatment of HIV-infected patients with 5-HT_{2A} antagonists is envisioned to prevent the spread of JC virus to the central nervous system and the development of PML. Aggressive therapeutic treatment of patients with PML is envisioned to reduce viral spread within the central nervous system and prevent additional episodes of demyelination.

35 One aspect of the present invention encompasses methods for the treatment of progressive multifocal leukoencephalopathy in an individual comprising administering to the

individual in need thereof a therapeutically effective amount of a compound according to any of the embodiments described herein or a pharmaceutical composition.

In some embodiments, the individual in need thereof has a lymphoproliferative disorder. In some embodiments, the lymphoproliferative disorder is leukemia or lymphoma. In some embodiments, the leukemia or lymphoma is chronic lymphocytic leukemia, Hodgkin's disease, or the like.

In some embodiments, the individual in need thereof has a myeloproliferative disorder.

In some embodiments, the individual in need thereof has carcinomatosis.

In some embodiments, the individual in need thereof has a granulomatous or inflammatory disease. In some embodiments, the granulomatous or inflammatory disease is tuberculosis or sarcoidosis.

In some embodiments, the individual in need thereof is immunocompromised. In some embodiments, the immunocompromised individual has impaired cellular immunity. In some embodiments, the impaired cellular immunity comprises impaired T-cell immunity.

In some embodiments, the individual in need thereof is infected with HIV. In some embodiments, the HIV-infected individual has a CD4⁺ cell count of $\leq 200/\text{mm}^3$. In some embodiments, the HIV-infected individual has AIDS. In some embodiments, the HIV-infected individual has AIDS-related complex (ARC). In certain embodiments, ARC is defined as the presence of two successive CD4⁺ cell counts below $200/\text{mm}^3$ and at least two of the following signs or symptoms: oral hairy leukoplakia, recurrent oral candidiasis, weight loss of at least 15 lb or 10% of body weight within last six months, multidermatomal herpes zoster, temperature above 38.5 °C for more than 14 consecutive days or more than 15 days in a 30-day period, or diarrhea with more than three liquid stools per day for at least 30 days [Yamada *et al. Clin. Diagn. Virol.* (1993) 1:245-256].

In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent [Mueller, *Ann. Thorac. Surg.* (2004) 77:354-362; and Krieger and Emre, *Pediatr. Transplantation* (2004) 8:594-599]. In some embodiments, the immunosuppressive therapy comprises administering an immunosuppressive agent selected from the group consisting of: corticosteroids (for example, prednisone and the like), calcineurin inhibitors (for example, cyclosporine, tacrolimus, and the like), antiproliferative agents (for example, azathioprine, mycophenolate mofetil, sirolimus, everolimus, and the like), T-cell depleting agents (for example, OKT[®]3 monoclonal antibody (mAb), anti-CD3 immunotoxin FN18-CRM9, Campath-1H (anti-CD52) mAb, anti-CD4 mAb, anti-T cell receptor mAb, and the like), anti-IL-2 receptor (CD25) mAb (for example, basiliximab, daclizumab, and the like), inhibitors of co-stimulation (for example, CTLA4-Ig, anti-CD154 (CD40 ligand) mAb, and the like), deoxyspergualin and analogs thereof (for example, 15-DSG,

LF-08-0299, LF14-0195, and the like), leflunomide and analogs thereof (for example, leflunomide, FK778, FK779, and the like), FTY720, anti-alpha-4-integrin monoclonal antibody, and anti-CD45 RB monoclonal antibody. In some embodiments, the immunosuppressive agent and said compound or pharmaceutical composition are administered in separate dosage forms. In some embodiments, the immunosuppressive agent and said compound or pharmaceutical composition are administered in a single dosage form.

In some embodiments, the individual in need thereof is undergoing immunosuppressive therapy after organ transplantation. In some embodiments, the organ is liver, kidney, lung, heart, or the like [Singh *et al. Transplantation* (2000) 69:467-472].

In some embodiments, the individual in need thereof is undergoing treatment for a rheumatic disease. In some embodiments, the rheumatic disease is systemic lupus erythematosus or the like.

In some embodiments, the compound or the pharmaceutical composition inhibits JC virus infection of human glial cells

9. Hypertension

Serotonin has been observed to play an important role in the regulation of vascular tone, vasoconstriction, and pulmonary hypertension (Deuchar, G. *et al. Pulm. Pharmacol. Ther.* 18(1):23-31. 2005; and Marcos, E. *et al. Circ. Res.* 94(9):1263-70 2004). Ketanserin, a 5-HT_{2A} inverse agonist, has been demonstrated to protect against circulatory shocks, intracranial hypertension, and cerebral ischemia during heatstroke (Chang, C. *et al. Shock* 24(4): 336-340 2005); and to stabilize blood pressure in spontaneously hypertensive rats (Miao, C. *Clin. Exp. Pharmacol. Physiol.* 30(3): 189-193). Mainserin, a 5-HT_{2A} inverse agonist, has been shown to prevent DOCA-salt induced hypertension in rats (Silva, A. *Eur. J. Pharmacol.* 518(2-3): 152-7 2005).

10. Pain

5-HT_{2A} inverse agonists are also effective for the treatment of pain. Sarpogrelate has been observed to provide a significant analgesic effect both on thermal induced pain in rats after intraperitoneal administration and on inflammatory pain in rats after either intrathecal or intraperitoneal administration (Nishiyama, T. *Eur. J. Pharmacol.* 516:18-22 2005). This same 5-HT_{2A} inverse agonist in humans has been shown to be an effective treatment for lower back pain, leg pain and numbness associated with sciatica brought on by lumbar disc herniation (Kanayama, M. *et al. J. Neurosurg.: Spine* 2:441-446 2005).

PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

5 Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compounds with liquids or finely divided solid carriers, or both, in the required proportions, and then, if necessary, forming the resulting mixture into a desired shape.

10 Conventional excipients, such as binding agents, fillers, acceptable wetting agents, tableting lubricants, and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions, and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-
15 aqueous vehicles (including edible oils), preservatives, and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before
20 filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see
25 Remington, *The Science and Practice of Pharmacy*, 20th Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*).

While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or
30 composition further comprising a pharmaceutically acceptable carrier.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers thereof and/or prophylactic ingredients. The carriers must be "acceptable" in the sense of being compatible with the other ingredients of
35 the formulation and not overly deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-

cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with a minimum of degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as 5-HT_{2A} serotonin receptor modulators. By the term "active ingredient" is defined in the context of a "pharmaceutical composition" and is intended to mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits, and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the

illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention.

Representative doses of the present invention include, but not limited to, about 0.001 mg to

5 about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg, and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4, doses. Depending on the individual and as deemed appropriate from the patient's physician
10 or caregiver it may be necessary to deviate upward or downward from the doses described herein.

The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient
15 and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to another, such as a mammal, preferably a human, however, more often, these extrapolations are
20 not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized, on whether an acute or chronic disease state is being
25 treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage regimen employed may vary widely and therefore may deviate from a preferred dosage
30 regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per
35 day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4, part administrations. If

appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable

preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles

comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation, this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others, and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or

ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

5 The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, 10 hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like, such as those pharmaceutically acceptable salts listed in *Journal of Pharmaceutical Sciences*, 66:1-19 (1977); incorporated herein by reference in its entirety.

15 The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

20 Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to 25 alter or to eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated 30 by reference in their entirety.

 Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable 35 carrier.

 It is noted that when the 5-HT_{2A} serotonin receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but

in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as 5-HT_{2A} serotonin receptor modulators, for the treatment of a 5-HT_{2A}-associated disease or disorder in domestic animals (e.g., cats and dogs) and in other domestic animals (e.g., cows, chickens, fish, etc.).

- 5 Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds of the
10 present invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the 5-HT_{2A} serotonin receptor in tissue samples, including human, and for identifying 5-HT_{2A} serotonin receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel 5-HT_{2A}-receptor assays of which comprise such radio-labeled compounds.

15 The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radio-labeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be
20 incorporated in compounds of the present invention include but are not limited to ²H (also written as D for deuterium), ³H (also written as T for tritium), ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ¹⁸F, ³⁵S, ³⁶Cl, ⁸²Br, ⁷⁵Br, ⁷⁶Br, ⁷⁷Br, ¹²³I, ¹²⁴I, ¹²⁵I and ¹³¹I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* 5-HT_{2A} serotonin receptor labeling and
25 competition assays, compounds that incorporate ^{3H}, ¹⁴C, ⁸²Br, ¹²⁵I, ¹³¹I or ³⁵S will generally be most useful. For radio-imaging applications ¹¹C, ¹⁸F, ¹²⁵I, ¹²³I, ¹²⁴I, ¹³¹I, ⁷⁵Br, ⁷⁶Br or ⁷⁷Br will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound of Formula (Ia) that has incorporated at least one radionuclide; in some embodiments the
30 radionuclide is selected from the group consisting of ^{3H}, ¹⁴C, ¹²⁵I, ³⁵S and ⁸²Br.

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide ^{3H} and/or ¹⁴C isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (i.e., ²H) may afford certain therapeutic advantages resulting from greater
35 metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in

the Drawings and Examples *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*.

Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the scarcer radio-isotope or nonradioactive isotope.

Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas - This procedure normally yields high specific activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [^3H] - This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

C. Reduction with Lithium Aluminum Hydride [^3H] - This procedure offers products at almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters, and the like.

D. Tritium Gas Exposure Labeling - This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. *N*-Methylation using Methyl Iodide [^3H] - This procedure is usually employed to prepare *O*-methyl or *N*-methyl (^3H) products by treating appropriate precursors with high specific activity methyl iodide (^3H). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of ^{125}I into target molecules include:

A. Sandmeyer and like reactions - This procedure transforms an aryl or heteroaryl amine into a diazonium salt, such as a tetrafluoroborate salt, and subsequently to ^{125}I labeled compound using Na^{125}I . A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

B. Ortho ^{125}I Iodination of phenols - This procedure allows for the incorporation of ^{125}I at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with ^{125}I - This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [i.e. $\text{Pd}(\text{Ph}_3\text{P})_4$] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [e.g., $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled 5-HT_{2A} serotonin receptor compound of Formula (Ia) can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (i.e., test compound) can be evaluated for its ability to reduce binding of the “radio-labeled compound of Formula (Ia)” to the 5-HT_{2A}-receptor. Accordingly, the ability of a test compound to compete with the “radio-labeled compound of Formula (Ia)” for the binding to the 5-HT_{2A} serotonin receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the 5-HT_{2A} serotonin receptor. In one embodiment the labeled compound has an IC₅₀ less than about 500 μM, in another embodiment the labeled compound has an IC₅₀ less than about 100 μM, in yet another embodiment the labeled compound has an IC₅₀ less than about 10 μM, in yet another embodiment the labeled compound has an IC₅₀ less than about 1 μM, and in still yet another embodiment the labeled inhibitor has an IC₅₀ less than about 0.1 μM.

Other uses of the disclosed receptors and methods will become apparent to those in the art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

EXAMPLES

Example 1: Syntheses of Compounds of the Present Invention.

Illustrated syntheses for compounds of the present invention are shown in Figures 1 through 5 where the symbols have the same definitions as used throughout this disclosure.

The compounds of the invention and their synthesis are further illustrated by the following examples. The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version 7.0.1, AutoNom version 2.2. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

Chemistry: Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, q = quartet, sx = sextet, sp = septet, m = multiplet, bs = broad

singlet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F₂₅₄ (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman), and column chromatography was carried out on a silica gel column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

LCMS specs: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source, AB/MDS Sciex; Software: Analyst 1.2.

Example 1.1: Preparation of {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 28).

Step A: Preparation of Intermediate *tert*-Butyl 4-(4-Fluorophenethyl)piperazine-1-carboxylate.

tert-Butyl piperazine-1-carboxylate (1.00 g, 5.37 mmol) was dissolved in DMF (20 mL). 1-(2-Bromoethyl)-4-fluorobenzene (2.62 g, 12.9 mmol) and potassium carbonate (2.23 g, 16.1 mmol) were then added to the solution. The reaction mixture was heated for 1 h at 120 °C under microwave irradiation in a heavy-walled sealed tube. The product was purified by HPLC (5-95% ACN/H₂O) to afford the TFA salt of the title compound (1.65 g, 84% purity) as a solid. Exact mass calculated for C₁₇H₂₅FN₂O₂: 308.2; Found: LCMS *m/z* = 309.4 (M+H⁺).

Step B: Preparation of Intermediate 1-(4-Fluorophenethyl)piperazine.

tert-Butyl 4-(4-fluorophenethyl)piperazine-1-carboxylate (1.65 g, 5.37 mmol) and 4 M HCl in dioxane (6 mL) were stirred at 43 °C for 1 h. The product was purified by HPLC (5-50% ACN/ H₂O) to afford the TFA salt of the title compound (510 mg) as a solid. Exact mass calculated for C₁₂H₁₇FN₂: 208.1; Found: LCMS *m/z* = 209.0 (M+H⁺).

Step C: Preparation of {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone.

1-(4-Fuorophenethyl)piperazine (68 mg, 0.33 mmol), 1-methyl-1*H*-indazole-3-carboxylic acid (63 mg, 0.36 mmol), HATU (162 mg, 0.42 mmol), triethylamine (228 µL, 1.64 mmol) and THF (2 mL) were heated for 15 min at 100 °C under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated under reduced pressure and the resulting oil was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (152 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.02-3.17 (m, 4H), 3.27-3.42 (m, 2H), 3.54-3.76 (m, 4H), 4.10 (s, 3H), 4.68-4.93 (m, 1H), 5.22-5.45 (m, 1H), 7.09 (t, *J* = 8.84 Hz, 2H), 7.26-7.32 (m, 3H), 7.48 (t, *J* = 7.58 Hz, 1H), 7.60 (d, *J* = 8.34 Hz,

1H), 8.09 (d, $J = 8.34$ Hz, 1H). Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS $m/z = 367.5$ ($M+H^+$).

Example 1.2: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(7-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 11).

Step A: Preparation of Intermediate *tert*-Butyl 4-(2-(4-Fluorophenyl)-2-oxoethyl)piperazine-1-carboxylate.

tert-Butyl piperazine-1-carboxylate (5.00 g, 26.8 mmol) was dissolved in DMF (15 mL). 2-Bromo-1-(4-fluorophenyl)ethanone (7.00 g, 32.2 mmol) and potassium carbonate (11.1 g, 80.5 mmol) were then added to the solution. The reaction mixture was stirred at room temperature for 10 min. The product was purified by HPLC (5-95% ACN/ H_2O) to afford the TFA salt of the title compound (9.06 g) as a solid. Exact mass calculated for $C_{17}H_{23}FN_2O_3$: 322.2; Found: LCMS $m/z = 323.2$ ($M+H^+$).

Step B: Preparation of Intermediate 1-(4-Fluorophenyl)-2-(piperazin-1-yl)ethanone.

tert-Butyl 4-(2-(4-fluorophenyl)-2-oxoethyl)piperazine-1-carboxylate (8.65 g, 26.8 mmol), 4 M HCl in dioxane (6 mL) and dioxane (20 mL) were stirred at 43 °C for 1 h. The solvent was removed under reduced pressure and dried in a vacuum oven to afford the title compound (5.29 g). Exact mass calculated for $C_{12}H_{15}FN_2O$: 222.1; Found: LCMS $m/z = 223.4$ ($M+H^+$).

Step C: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(7-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone.

1-(4-Fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59 mg, 0.20 mmol), 7-methoxy-3a,7a-dihydro-1*H*-indazole-3-carboxylic acid (50 mg, 0.26 mmol), HATU (99 mg, 0.26 mmol), triethylamine (139 μ L, 1.00 mmol) and THF (2 mL) were heated for 20 min at 100 °C under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated under reduced pressure and the resulting oil was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (64 mg) as a solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 3.38-3.56 (m, 4H), 3.99 (s, 3H), 4.04-4.29 (m, 2H), 4.37-4.63 (m, 2H), 4.73 (s, 2H), 6.88 (d, $J = 7.83$ Hz, 1H), 7.19 (t, $J = 7.83$ Hz, 1H), 7.30 (t, $J = 8.84$ Hz, 2H), 7.62 (d, $J = 8.34$ Hz, 1H), 8.01 (dd, $J = 5.31, 8.84$ Hz, 2H). Exact mass calculated for $C_{21}H_{21}FN_4O_3$: 396.2; Found: LCMS $m/z = 397.4$ ($M+H^+$).

Example 1.3: Preparation of 2-[4-(6-Fluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 7).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59 mg, 0.20 mmol), and

6-fluoro-1*H*-indazole-3-carboxylic acid (47 mg, 0.26 mmol) as starting materials, to afford the TFA salt (61 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.56-2.66 (m, 4H), 3.67-3.78 (m, 2H), 3.92 (s, 2H), 3.97-4.06 (m, 2H), 7.10 (td, *J* = 9.35, 2.02 Hz, 1H), 7.35 (t, *J* = 8.84 Hz, 2H), 7.40 (dd, *J* = 9.35, 2.02 Hz, 1H), 7.98 (dd, *J* = 8.84, 5.31 Hz, 1H), 8.09 (dd, *J* = 5.31, 8.84 Hz, 2H). Exact mass calculated for C₂₀H₁₈F₂N₄O₂: 384.1; Found: LCMS *m/z* = 385.3 (M+H⁺).

Example 1.4: Preparation of 2-[4-(5-Chloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 3).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59 mg, 0.20 mmol), and 5-chloro-1*H*-indazole-3-carboxylic acid (51 mg, 0.26 mmol) as starting materials, to afford the TFA salt (16 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.41-3.56 (m, 4H), 4.00-4.27 (m, 2H), 4.44-4.67 (m, 2H), 4.80 (s, 2H), 7.31 (t, *J* = 8.84 Hz, 2H), 7.43 (dd, *J* = 8.84, 2.02 Hz, 1H), 7.62 (dd, *J* = 8.84, 2.53 Hz, 1H), 8.03 (dd, *J* = 5.31, 8.84 Hz, 2H), 8.10 (d, *J* = 2.02 Hz, 1H). Exact mass calculated for C₂₀H₁₈ClFN₄O₂: 400.1; Found: LCMS *m/z* = 401.5 (M+H⁺).

Example 1.5: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(6-trifluoromethoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 29).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (85 mg, 0.29 mmol), and 6-(trifluoromethoxy)-1*H*-indazole-3-carboxylic acid (92 mg, 0.37 mmol) as starting materials, to afford the TFA salt (45 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 3.52-3.69 (m, 4H), 4.01-4.53 (m, 4H), 5.06 (s, 2H), 7.22 (t, *J* = 9.09 Hz, 1H), 7.35 (t, *J* = 8.59 Hz, 2H), 7.53 (s, 1H), 8.09-8.16 (m, 2H), 8.18 (d, *J* = 9.09 Hz, 1H). Exact mass calculated for C₂₁H₁₈F₄N₄O₃: 450.1; Found: LCMS *m/z* = 451.4 (M+H⁺).

Example 1.6: Preparation of 2-[4-(1-Ethyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 8).

1-(4-Fluoro-phenyl)-2-[4-(1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (74 mg, 0.20 mmol), bromoethane (38 mg, 0.34 mmol), potassium carbonate (33 mg, 0.24 mmol) and DMF (2 mL) were heated for 30 min at 100 °C under microwave irradiation in a heavy-walled sealed tube. The product was purified by preparative HPLC to afford the TFA salt of the title compound (12 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 1.53 (t, *J* = 7.33 Hz, 3H), 3.52-3.68 (m, 4H), 3.93-4.45 (m, 4H), 4.54 (q, *J* = 7.33 Hz, 2H), 5.05 (s, 2H), 7.27-7.38 (m,

3H), 7.49 (t, $J = 8.34$ Hz, 1H), 7.67 (d, $J = 8.34$ Hz, 1H), 8.06-8.16 (m, 3H). Exact mass calculated for $C_{22}H_{23}FN_4O_2$: 394.2; Found: LCMS $m/z = 395.4$ ($M+H^+$).

Example 1.7: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(1-isopropyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 4).

5 **Step A: Preparation of Intermediate 1-Isopropyl-1H-indazole-3-carboxylic acid.**

To potassium hydroxide pellets (9.34 g, 167 mmol) in DMSO (30 mL) under a nitrogen atmosphere at room temperature was added 1H-indazole-3-carboxylic acid (5.0 g, 30.8 mmol). The resulting mixture was stirred at room temperature for 45 min before 2-iodopropane (1.71 mL, 89.4 mmol) was added while keeping the reaction temperature near 25 °C. The resulting
10 solution was stirred at room temperature for 1.5 h before it was poured into ice cold water (400 mL). Glacial acetic acid (10.0 mL) was added and the resulting precipitate was collected by filtration. The filtrate was extracted three times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude solid. The crude solid was purified by preparative HPLC using a gradient 0-35 %
15 ACN/H₂O and 1% TFA to afford the TFA salt of the title compound (1.56 g) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 1.61 (d, $J = 6.57$ Hz, 6H), 5.07 (sp, $J = 6.57$ Hz, 1H), 7.31 (t, $J = 7.58$ Hz, 1H), 7.46 (t, $J = 7.58$ Hz, 1H), 7.69 (d, $J = 8.59$ Hz, 1H), 8.15 (d, $J = 8.59$ Hz, 1H). Exact mass calculated for $C_{11}H_{12}N_2O_2$: 204.1; Found: LCMS $m/z = 205.2$ ($M+H^+$).

20 **Step B: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(1-isopropyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone.**

The title compound was prepared in a similar manner as described in Example 1.2, Step C, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59 mg, 0.20 mmol), and 1-isopropyl-1H-indazole-3-carboxylic acid (45 mg, 0.22 mmol) as starting materials, to afford the TFA salt (94 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 1.60 (d, $J = 6.57$
25 Hz, 6H), 3.53-3.67 (m, 4H), 3.88-4.49 (m, 4H), 5.05 (s, 2H), 5.07 (sp, $J = 6.57$ Hz, 1H), 7.30 (t, $J = 7.58$ Hz, 1H), 7.35 (t, $J = 8.59$ Hz, 2H), 7.48 (t, $J = 7.58$ Hz, 1H), 7.70 (d, $J = 8.59$ Hz, 1H), 8.10 (d, $J = 8.59$ Hz, 1H), 8.11-8.17 (m, 2H). Exact mass calculated for $C_{23}H_{25}FN_4O_2$: 408.2; Found: LCMS $m/z = 409.5$ ($M+H^+$).

30 **Example 1.8: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(1-propyl-1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 30).**

The title compound was prepared in a similar manner as described in Example 1.7, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (25 mg, 0.085 mmol), and 1-propyl-1H-indazole-3-carboxylic acid (17 mg, 0.08 mmol) as starting materials, to afford the
35 TFA salt (41 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 0.92 (t, $J = 7.33$ Hz, 3H), 1.98 (se, $J = 7.33$ Hz, 2H), 3.52-3.68 (m, 4H), 3.93-4.61 (m, 4H), 4.47 (t, $J = 7.07$ Hz, 2H), 5.05 (s, 2H), 7.30 (t, $J = 7.58$ Hz, 1H), 7.35 (t, $J = 8.59$ Hz, 2H), 7.49 (t, $J = 7.58$ Hz, 1H), 7.67

(d, $J = 8.59$ Hz, 1H), 8.10 (d, $J = 8.59$ Hz, 1H), 8.11-8.17 (m, 2H). Exact mass calculated for $C_{23}H_{25}FN_4O_2$: 408.2; Found: LCMS $m/z = 409.6$ ($M+H^+$).

Example 1.9: Preparation of 2-[4-(5-Bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 25).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (200 mg, 0.678 mmol), and 5-bromo-1*H*-indazole-3-carboxylic acid (180 mg, 0.74 mmol) as starting materials, to afford the TFA salt (196 mg) as a solid. 1H NMR (Methanol- d_4 , 400 MHz) δ 2.56-2.68 (m, 4H), 3.68-3.78 (m, 2H), 3.92 (s, 2H), 4.00-4.10 (m, 2H), 7.36 (t, $J = 8.84$ Hz, 2H), 7.54 (dd, $J = 1.77, 8.84$ Hz, 1H), 7.61 (d, $J = 8.84$ Hz, 1H), 8.06-8.11 (m, 2H), 8.15 (d, $J = 1.77$ Hz, 1H). Exact mass calculated for $C_{20}H_{18}BrFN_4O_2$: 444.1; Found: LCMS m/z (%) = 445.2 ($M+H^+ ^{79}Br$, 100%), 447.2($M+H^+ ^{81}Br$, 98%).

Example 1.10: Preparation of 2-[4-(6-Bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 21).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (200 mg, 0.678 mmol), and 6-bromo-1*H*-indazole-3-carboxylic acid (180 mg, 0.74 mmol) as starting materials, to afford the TFA salt (166 mg) as a solid. 1H NMR (Methanol- d_4 , 400 MHz) δ 2.56-2.67 (m, 4H), 3.68-3.76 (m, 2H), 3.92 (s, 2H), 3.96-4.05 (m, 2H), 7.32-7.40 (m, 3H), 7.85 (s, 1H), 7.91 (d, $J = 8.59$ Hz, 1H), 8.05-8.11 (m, 2H). Exact mass calculated for $C_{20}H_{18}BrFN_4O_2$: 444.1; Found: LCMS m/z (%) = 445.2 ($M+H^+ ^{79}Br$, 100%), 447.2($M+H^+ ^{81}Br$, 98%).

Example 1.11: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(6-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 17).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60 mg, 0.20 mmol), and 6-methoxy-1*H*-indazole-3-carboxylic acid (43 mg, 0.22 mmol) as starting materials, to afford the TFA salt (45 mg) as a solid. 1H NMR (Methanol- d_4 , 400 MHz) δ 2.68-2.82 (m, 4H), 3.87 (s, 3H), 3.89-3.94 (m, 2H), 4.02 (s, 2H), 4.08-4.14 (m, 2H), 6.88 (dd, $J = 2.27, 9.09$ Hz, 1H), 6.97 (d, $J = 2.27$ Hz, 1H), 7.24 (t, $J = 8.84$ Hz, 2H), 7.79 (d, $J = 9.09$ Hz, 1H), 8.08-8.14 (m, 2H). Exact mass calculated for $C_{21}H_{21}FN_4O_3$: 396.2; Found: LCMS $m/z = 397.2$ ($M+H^+$).

Example 1.12: Preparation of 2-[4-(6-Chloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 13).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60 mg, 0.20 mmol), and 6-chloro-1*H*-indazole-3-carboxylic acid (44 mg, 0.22 mmol) as starting materials, to afford the TFA salt (66 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 2.56-2.67 (m, 4H), 3.68-3.76 (m, 2H), 3.92 (s, 2H), 3.97-4.04 (m, 2H), 7.24 (dd, *J* = 2.02, 8.84 Hz, 1H), 7.35 (t, *J* = 8.84 Hz, 2H), 7.70 (d, *J* = 1.52 Hz, 1H), 7.97 (d, *J* = 8.84 Hz, 1H), 8.06-8.12 (m, 2H). Exact mass calculated for C₂₀H₁₈ClFN₄O₂: 400.1; Found: LCMS *m/z* = 401.5 (M+H⁺).

Example 1.13: Preparation of 2-[4-(1-Cyclopentyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 9).

The title compound was prepared in a similar manner as described in Example 1.7, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59 mg, 0.20 mmol), and 1-cyclopentyl-1*H*-indazole-3-carboxylic acid (51 mg, 0.22 mmol) as starting materials, to afford the TFA salt (85 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 1.75-1.87 (m, 2H), 1.89-2.01 (m, 2H), 2.08-2.19 (m, 2H), 2.20-2.30 (m, 2H), 3.50-3.68 (m, 4H), 3.86-4.54 (m, 4H), 5.05 (s, 2H), 5.20-5.29 (m, 1H), 7.29 (t, *J* = 7.58 Hz, 1H), 7.35 (t, *J* = 8.84 Hz, 2H), 7.48 (t, *J* = 7.58 Hz, 1H), 7.71 (d, *J* = 8.84 Hz, 1H), 8.09 (dd, *J* = 0.76, 8.08 Hz, 1H), 8.13 (dd, *J* = 5.31, 8.84 Hz, 2H). Exact mass calculated for C₂₅H₂₇FN₄O₂: 434.2; Found: LCMS *m/z* = 435.4 (M+H⁺).

Example 1.14: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(5-*o*-tolyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 34).

2-[4-(5-Bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (60 mg, 0.13 mmol), *o*-tolylboronic acid (27 mg, 0.20 mmol), potassium carbonate (56 mg, 0.40 mmol), tetrakis(triphenylphosphine)palladium(0) (16 mg, 0.014 mmol) and THF (1.5 mL) were heated to 120 °C for 1.5 h under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated and the resulting solid was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (42 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.26 (s, 3H), 3.38-3.65 (m, 4H), 3.95-4.04 (m, 2H), 4.05-4.34 (m, 2H), 4.76 (s, 2H), 7.25-7.30 (m, 4H), 7.31 (t, *J* = 8.84 Hz, 2H), 7.43 (dd, *J* = 1.52, 8.59 Hz, 1H), 7.68 (d, *J* = 8.59 Hz, 1H), 7.99-8.05 (m, 3H). Exact mass calculated for C₂₇H₂₅FN₄O₂: 456.2; Found: LCMS *m/z* = 457.5 (M+H⁺).

Example 1.15: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(6-*o*-tolyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 31).

The title compound was prepared in a similar manner as described in Example 1.14, using 2-[4-(6-bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone

(60 mg, 0.13 mmol), and *o*-tolylboronic acid (27 mg, 0.20 mmol) as starting materials, to afford the TFA salt (11 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.26 (s, 3H), 3.35-3.64 (m, 4H), 3.95-4.04 (m, 2H), 4.05-4.34 (m, 2H), 4.78 (s, 2H), 7.25 (d, *J* = 8.59 Hz, 1H), 7.27-7.35 (m, 6H), 7.54 (s, 1H), 8.00-8.06 (m, 2H), 8.12 (d, *J* = 8.59 Hz, 1H). Exact mass calculated for C₂₇H₂₅FN₄O₂: 456.2; Found: LCMS *m/z* = 457.4 (M+H⁺).

Example 1.16: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(6-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 26).

The title compound was prepared in a similar manner as described in Example 1.14 using 2-[4-(6-bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (60 mg, 0.13 mmol), and methylboronic acid (24 mg, 0.4 mmol) as starting materials, to afford the TFA salt (5 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.48 (s, 3H), 3.34-3.46 (m, 4H), 3.94-4.26 (m, 2H), 4.37-4.60 (m, 2H), 4.65 (s, 2H), 7.12 (d, *J* = 8.34 Hz, 1H), 7.29 (t, *J* = 8.84 Hz, 2H), 7.40 (s, 1H), 7.95 (d, *J* = 8.34 Hz, 1H), 7.99-8.05 (m, 2H). Exact mass calculated for C₂₁H₂₁FN₄O₂: 380.2; Found: LCMS *m/z* = 381.4 (M+H⁺).

Example 1.17: Preparation of 2-[4-(6-Bromo-1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 22).

The title compound was prepared in a similar manner as described in Example 1.7, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (70 mg, 0.24 mmol), and 6-bromo-1-methyl-1*H*-indazole-3-carboxylic acid (67 mg, 0.26 mmol) as starting materials, to afford the TFA salt (122 mg) as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 3.17-3.72 (m, 5H), 3.80-4.03 (m, 1H), 4.12 (s, 3H), 4.41-4.71 (m, 1H), 4.81-5.00 (m, 1H), 5.09 (s, 2H), 7.43 (dd, *J* = 1.52, 8.59 Hz, 1H), 7.49 (t, *J* = 8.84 Hz, 2H), 7.97 (d, *J* = 8.59 Hz, 1H), 8.06-8.12 (m, 2H), 8.15 (d, *J* = 1.52 Hz, 1H). Exact mass calculated for C₂₁H₂₀BrFN₄O₂: 458.1; Found: LCMS *m/z* (%) = 459.2 (M+H⁺ ⁷⁹Br, 100%), 461.2 (M+H⁺ ⁸¹Br, 98%).

Example 1.18: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(5-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 14).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (100 mg, 0.339 mmol), and 5-methoxy-1*H*-indazole-3-carboxylic acid (72 mg, 0.37 mmol) as starting materials, to afford the TFA salt (73 mg) as a solid. ¹H NMR (Methanol-*d*₄, 400 MHz) δ 3.52-3.63 (m, 4H), 3.86 (s, 3H), 4.06-4.49 (m, 4H), 5.05 (s, 2H), 7.11 (dd, *J* = 2.27, 9.35 Hz, 1H), 7.34 (t, *J* = 8.59 Hz, 2H), 7.49 (s, 1H), 7.50 (d, *J* = 5.59 Hz, 1H), 8.09-8.16 (m, 2H). Exact mass calculated for C₂₁H₂₁FN₄O₃: 396.2; Found: LCMS *m/z* = 397.4 (M+H⁺).

Example 1.19: Preparation of 2-[4-(5,6-Dimethoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 10).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (118 mg, 0.400 mmol), and 5,6-dimethoxy-1*H*-indazole-3-carboxylic acid (116 mg, 0.52 mmol) as starting materials, to afford the TFA salt (88 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.35-3.58 (m, 4H), 3.86 (s, 3H), 3.88 (s, 3H), 3.96-4.35 (m, 2H), 4.43-4.67 (m, 2H), 4.74 (s, 2H), 7.04 (s, 1H), 7.30 (t, *J* = 8.84 Hz, 2H), 7.46 (s, 1H), 7.99-8.04 (m, 2H). Exact mass calculated for C₂₂H₂₃FN₄O₄: 426.2; Found: LCMS *m/z* = 427.4 (M+H⁺).

Example 1.20: Preparation of 2-[4-(6-Bromo-2-methyl-2*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 6).

The title compound was prepared in a similar manner as described in Example 1.7 using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (49 mg, 0.17 mmol) and 6-bromo-2-methyl-2*H*-indazole-3-carboxylic acid (47 mg, 0.18 mmol) as starting materials, to afford the TFA salt (65 mg) as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 3.21-3.87 (m, 8H), 4.20 (s, 3H), 5.02 (s, 2H), 7.32 (dd, *J* = 1.52, 8.84 Hz, 1H), 7.48 (t, *J* = 8.84 Hz, 2H), 7.69 (d, *J* = 9.09 Hz, 1H), 8.01 (d, *J* = 1.52 Hz, 1H), 8.06-8.12 (m, 2H). Exact mass calculated for C₂₁H₂₀BrFN₄O₂: 458.1; Found: LCMS *m/z* (%) = 459.2 (M+H⁺ ⁷⁹Br, 100%), 461.2 (M+H⁺ ⁸¹Br, 98%).

Example 1.21: Preparation of 3-{4-[2-(4-Fluoro-phenyl)-2-oxo-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile (Compound 2).

2-[4-(6-Bromo-1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (50 mg, 0.11 mmol), zinc cyanide (13 mg, 0.11 mmol), triethylamine (15 μL, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (3.8 mg, 0.003 mmol) and DMF (1.5 mL) were heated to 120 °C for 10 min under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated and the resulting solid was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (28 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.39-3.60 (m, 4H), 4.01-4.26 (m, 2H), 4.14 (s, 3H), 4.41-4.69 (m, 2H), 5.08 (s, 2H), 7.32 (t, *J* = 8.84 Hz, 2H), 7.52 (d, *J* = 8.59 Hz, 1H), 7.99-8.06 (m, 2H), 8.12 (s, 1H), 8.24 (d, *J* = 8.59 Hz, 1H). Exact mass calculated for C₂₂H₂₀FN₅O₂: 405.2; Found: LCMS *m/z* = 406.5 (M+H⁺).

Example 1.22: Preparation of 1-(4-Fluoro-phenyl)-2-[(*S*)-4-(1*H*-indazole-3-carbonyl)-2-methyl-piperazin-1-yl]-ethanone (Compound 1).

Step A: Preparation of Intermediate (*S*)-*tert*-Butyl 4-(2-(4-Fluorophenyl)-2-oxoethyl)-3-methylpiperazine-1-carboxylate.

(*S*)-*tert*-Butyl-3-methylpiperazine-1-carboxylate (1.00 g, 4.99 mmol), 2-bromo-1-(4-fluorophenyl)ethanone (1.14 g, 5.24 mmol) and triethylamine (1.04 mL, 7.49 mmol) were dissolved in DMA (5 mL) and stirred for 10 min at room temperature. The crude mixture was purified by preparative HPLC to afford the TFA salt of the title compound (0.980 g) as an oil. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 1.13 (s, 3H), 1.42 (s, 9H) 2.47 (t, *J* = 5.0 Hz, 4H), 3.36 (t, *J* = 5.0 Hz, 3H), 3.77 (s, 2H), 7.29 (m, 2H), 8.11 (m, 2H). Exact mass calculated for C₁₈H₂₅FN₂O₃: 336.2; Found: LCMS *m/z* = 337.4 (M+H⁺).

Step B: Preparation of Intermediate (*S*)-1-(4-Fluorophenyl)-2-(2-methylpiperazin-1-yl)ethanone.

(*S*)-*tert*-Butyl 4-(2-(4-fluorophenyl)-2-oxoethyl)-3-methylpiperazine-1-carboxylate from Step A was dissolved in 4 M HCl in dioxane (5 mL) and stirred at 45 °C for 20 min. The solvent was removed under reduced pressure to afford the dihydrochloride salt of the title compound (892 mg) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 1.47 (s, 3H), 3.58-3.78 (m, 5H), 3.82-3.96 (m, 1H), 4.11 (s, 1H), 5.07-5.33 (dd, *J* = 7.9, 59.0 Hz 2H), 7.31 (m, 2H), 8.15 (m, 2H). Exact mass calculated for C₁₃H₁₇FN₂O: 236.1; Found: LCMS *m/z* = 237.2 (M+H⁺).

Step C: Preparation of 1-(4-Fluoro-phenyl)-2-[(*S*)-4-(1*H*-indazole-3-carbonyl)-2-methyl-piperazin-1-yl]-ethanone.

(*S*)-1-(4-Fluorophenyl)-2-(methylpiperazin-1-yl)ethanone dihydrochloride (50 mg, 162 μmol) was added to a solution of 1*H*-indazole-3-carboxylic acid (34.1, 210 μmol), HATU (79.9 mg, 210 μmol) and triethylamine (112 μl, 809 μmol) in THF (3.0 mL). The reaction mixture was heated to 100 °C under microwave irradiation for 20 min. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC to afford the TFA salt of the title compound (24.6 mg) as a solid. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 1.34-1.48 (m, 3H) 3.30 (s, 1H), 3.35-3.47 (s, 2H), 3.50-3.65 (s, 2H), 3.71-3.85 (s, 2H), 4.65-4.75 (dd, *J* = 7.9, 18.0 Hz, 1H), 4.76-4.87 (d, *J* = 18.0 Hz, 1H), 7.30 (m, 3H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 8.07 (m, 3H). Exact mass calculated for C₂₁H₂₁FN₄O₂: 380.2; Found: LCMS *m/z* = 381.4 (M+H⁺).

Example 1.23: Preparation of 1-(4-Fluoro-phenyl)-2-[(*S*)-2-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 5).

The title compound was prepared in a similar manner as described in Example 1.22, Step C, using 1-methyl-1*H*-indazole-3-carboxylic acid (55.6 mg, 315 μmol) and (*S*)-1-(4-fluorophenyl)-2-(2-methylpiperazin-1-yl)ethanone dihydrochloride (75 mg, 243 μmol) as starting materials, to afford the TFA salt (7.1 mg) as a solid. ¹H NMR (400 MHz, Acetonitrile-

d_3) δ 1.43 (s, 3H), 2.90-3.25 (s, 4H), 3.43 (s, 1H), 3.57 (s, 1H), 3.80 (s, 1H) 4.10 (s, 3H), 4.70 (d, J = 18.0 Hz, 1H), 4.81 (d, J = 18.0 Hz, 1H), 7.30 (m, 3H), 7.48 (t, J = 7.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 8.06 (m, 3H). Exact mass calculated for $C_{22}H_{23}FN_4O_2$: 394.2; Found: LCMS m/z = 395.4 ($M+H^+$).

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Example 1.24: Preparation of 1-(4-Fluoro-phenyl)-2-[(*S*)-3-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 18).

The starting material, (*S*)-1-(4-fluorophenyl)-2-(3-methylpiperazin-1-yl)ethanone dihydrochloride, was made in a similar manner as described in Example 1.22, Steps A and B, using (*S*)-*tert*-butyl 2-methylpiperazine-1-carboxylate (1.00 g, 4.99 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (1.14 g, 5.24 mmol).

The title compound was made in a similar manner as described in Example 1.22, Step C, using (*S*)-1-(4-fluorophenyl)-2-(3-methylpiperazin-1-yl)ethanone dihydrochloride (60.0 mg, 194 μ mol), and 1-methyl-1*H*-indazole-3-carboxylic acid (44.4 mg, 252 μ mol) as starting materials, to afford the TFA salt of the title compound (1.0 mg) as a solid. 1H NMR (400 MHz, Acetonitrile- d_3) δ 1.58 (s, 3H), 2.25-2.45 (s, 4H), 3.20 (m, 1H), 3.57 (s, 1H), 3.58 (m, 1H), 4.10 (s, 3H), 4.57 (d, J = 18.0 Hz, 1H), 4.72 (d, J = 18.0 Hz, 1H), 7.30 (m, 3H), 7.50 (t, J = 7.9 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 8.07 (m, 3H). Exact mass calculated for $C_{22}H_{23}FN_4O_2$: 394.2; Found: LCMS m/z = 395.5 ($M+H^+$).

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Example 1.25: Preparation of {(*R*)-4-[2-(4-Fluoro-phenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone (Compound 33).

1*H*-Indazole-3-carboxylic acid (48.6 mg, 299.7 μ mol) and (*R*)-1-(4-fluorophenethyl)-2-methylpiperazine (56.3 mg, 253.3 μ mol) were dissolved in DMA (3 mL) and DIEA (50 μ L). HATU (104.9 mg, 275.9 μ mol) was added. The stirring was continued for 2 h. The reaction product was purified by HPLC to afford the TFA salt of the title compound (74 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS m/z = 367.5 ($M+H^+$).

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Example 1.26: Preparation of {(*S*)-4-[2-(4-Fluoro-phenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone (Compound 24).

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1*H*-Indazole-3-carboxylic acid (48.6 mg, 300 μ mol) and (*S*)-1-(4-fluorophenethyl)-2-methylpiperazine (55.1 mg, 248 μ mol) were dissolved in DMA (3 mL) and DIEA (50 μ L). HATU (110 mg, 289 μ mol) was added. The stirring was continued for 2 h. The reaction product was purified by HPLC to afford the TFA salt of the title compound (57 mg) as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ 1.21-1.49 (m, 3H), 2.84-4.00 (m, 9H), 4.39-4.74 (m, 1H), 4.90-5.26 (m, 1H), 7.20 (t, J = 8.78 Hz, 2H), 7.26 (t, J = 7.76 Hz, 1H), 7.32-7.42 (m, 2H),

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7.45 (t, $J = 7.80$ Hz, 1H), 7.65 (d, $J = 8.41$ Hz, 1H), 8.05 (d, $J = 8.07$ Hz, 1H), 9.83-10.17 (m, 1H). Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS $m/z = 367.5$ ($M+H^+$).

Example 1.27: Preparation of {(R)-4-[2-(4-Fluoro-phenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1H-indazol-3-yl)-methanone (Compound 20).

1H-Indazole-3-carboxylic acid (50.0 mg, 308 μ mol) and (R)-1-(4-fluorophenethyl)-3-methylpiperazine (60.6 mg, 273 μ mol) were dissolved in DMA (3 mL) and DIEA (50 μ L). HATU (110 mg, 289 μ mol) was added and stirring continued for 2 h. The product was purified by HPLC to afford the TFA salt of the title compound (31 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS $m/z = 367.5$ ($M+H^+$).

Example 1.28: Preparation of {(S)-4-[2-(4-Fluoro-phenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1H-indazol-3-yl)-methanone (Compound 16).

1H-Indazole-3-carboxylic acid (50.0 mg, 308 μ mol) and (S)-1-(4-fluorophenethyl)-3-methylpiperazine (60.6 mg, 273 μ mol) were dissolved in DMA (3 mL) and DIEA (50 μ L). HATU (110 mg, 289 μ mol) was added and stirring continued for 2 h. The product was purified by HPLC to afford the TFA salt of the title compound (6.0 mg) as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ 1.28-1.58 (m, 3H), 2.85-4.00 (m, 9H), 4.61-5.65 (m, 2H), 7.20 (t, $J = 8.87$ Hz, 2H), 7.26 (t, $J = 7.76$ Hz, 1H), 7.29-7.37 (m, 2H), 7.45 (t, $J = 7.81$ Hz, 1H), 7.65 (d, $J = 8.44$ Hz, 1H), 8.03 (d, $J = 8.17$ Hz, 1H), 9.64-9.95 (m, 1H). Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS $m/z = 367.4$ ($M+H^+$).

Example 1.29: Preparation of {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1H-indazol-3-yl)-methanone (Compound 23).

The title compound was prepared in a similar manner as described in Example 1.2, using 1H-indazole-3-carboxylic acid (41 mg, 0.253 mmol) as starting material, to afford the TFA salt (63 mg) as an off-white solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 2.42-2.62 (m, 2H), 3.11-3.16 (m, 4H), 3.32-3.36 (m, 4H), 3.61-3.74 (m, 2H), 7.12-7.17 (m, 2H), 7.31-7.37 (m, 3H), 7.49-7.54 (m, 1H), 7.68-7.70 (m, 1H), 8.14-8.16 (m, 1H). Exact mass calculated for $C_{20}H_{21}FN_4O$: 352.2; Found: LCMS $m/z = 353.3$ ($M+H^+$).

Example 1.30: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(1H-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 19).

The title compound was prepared in a similar manner as described in Example 1.2, using 1H-indazole-3-carboxylic acid (664 mg, 4.1 mmol) and 1-(4-fluoro-phenyl)-2-piperazin-1-yl-ethanone (1.33 g, 4.51 mmol) as starting materials, to afford the TFA salt (458 mg) as an off-white solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 3.41-3.60 (m, 4H), 4.00-4.42 (m, 4H),

4.81 (s, 2H), 7.31-7.40 (m, 3H), 7.49-7.54 (m, 1H), 7.67-7.72 (m, 1H), 8.05-8.12 (m, 2H), 8.15-8.18 (m, 1H). Exact mass calculated for $C_{20}H_{19}FN_4O_2$: 366.2; Found: LCMS m/z = 367.4 ($M+H^+$).

5 **Example 1.31: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 15).**

The title compound was prepared in a similar manner as described in Example 1.2, using 1-methyl-1*H*-indazole-3-carboxylic acid (352 mg, 2.00 mmol) and 1-(4-fluoro-phenyl)-2-piperazin-1-yl-ethanone (649 mg, 2.20 mmol) as starting materials, to afford the TFA salt (865 mg) as a light yellow solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 2.21-2.60 (m, 4H), 3.54 (bs, 4H), 4.17 (s, 3H), 4.83 (s, 2H), 7.34-7.41 (m, 3H), 7.53-7.57 (m, 1H), 7.66-7.68 (m, 1H), 8.08-8.12 (m, 2H), 8.16-8.19 (m, 1H). Exact mass calculated for $C_{21}H_{21}FN_4O_2$: 380.2; Found: LCMS m/z = 381.4 ($M+H^+$).

15 **Example 1.32: Preparation of 1-(4-Fluoro-phenyl)-2-{4-[1-(1*H*-indazole-3-carbonyl)-1*H*-indazole-3-carbonyl]-piperazin-1-yl}-ethanone (Compound 12).**

The title compound was prepared in a similar manner as described in Example 1.2, using 1*H*-indazole-3-carboxylic acid (664 mg, 4.10 mmol) and 1-(4-fluoro-phenyl)-2-piperazin-1-yl-ethanone (1.33 g, 4.51 mmol) as starting materials, to afford the TFA salt (22 mg) as an off-white solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 3.47-3.60 (m, 4H), 4.10-4.30 (m, 4H), 4.80 (s, 2H), 7.35-7.46 (m, 3H), 7.54-7.63 (m, 2H), 7.76-7.81 (m, 2H), 8.07-8.10 (m, 2H), 8.22-8.28 (m, 2H), 8.61-8.63 (m, 1H). Exact mass calculated for $C_{28}H_{23}FN_6O_3$: 510.2; Found: LCMS m/z = 511.5 ($M+H^+$).

25 **Example 1.33: Preparation of 2-[4-(1-Benzenesulfonyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 32).**

To the solution of benzene sulfonyl chloride (109 mg, 0.616 mmol) and triethylamine (62.4 mg, 0.616 mmol) in THF was added 1*H*-indazole-3-carboxylic acid (100 mg, 0.616 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, quenched with H_2O and extracted with ethyl acetate. The combined organic layer was dried and concentrated under reduced pressure. The crude product was then coupled with 1-(4-fluoro-phenyl)-2-piperazin-1-yl-ethanone dihydrochloride (100 mg, 0.339 mmol) using HATU (125 mg, 0.330 mmol) and triethylamine (0.2 mL) in DMF (1.5 mL). The mixture was heated under microwave irradiation at 100 °C for 10 min. The crude product was purified by HPLC to afford the TFA salt of the title compound (35 mg) as a light yellow solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 3.40-3.55 (m, 4H), 4.20 (s, 4H), 4.76 (s, 2H), 7.35-7.40 (m, 2H), 7.52-7.55 (m, 1H), 7.60-7.64 (m,

2H), 7.73-7.79 (m, 2H), 8.05-8.11 (m, 5H), 8.28-8.30 (m, 1H). Exact mass calculated for $C_{26}H_{23}FN_4O_4S$: 506.1; Found: LCMS m/z = 507.3 ($M+H^+$).

Example 1.34: Preparation of 2-{4-[1-(4-Fluoro-benzoyl)-1*H*-indazole-3-carbonyl]-piperazin-1-yl}-1-(4-fluoro-phenyl)-ethanone (Compound 27).

The title compound was prepared in a similar manner as described in Example 1.33, using 4-fluorobenzoyl chloride (158 mg, 0.616 mmol) as starting material, to afford the TFA salt (16 mg) as a white solid. 1H NMR (Acetonitrile- d_3 , 400 MHz) δ 3.40-3.55 (m, 4H), 4.20-4.33 (m, 4H), 4.76 (s, 2H), 7.35-7.40 (m, 4H), 7.60-7.63 (m, 1H), 7.77-7.81 (m, 2H), 8.07-8.11 (m, 2H), 8.15-8.19 (m, 2H), 8.57-8.59 (m, 1H). Exact mass calculated for $C_{27}H_{22}F_2N_4O_3$: 488.2; Found: LCMS m/z = 489.3 ($M+H^+$).

Example 1.35: Preparation of {4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 53).

Step A: Preparation of *tert*-Butyl 4-(2-(2,4-Difluorophenyl)acetyl)piperazine-1-carboxylate.

2-(2,4-Difluorophenyl)acetic acid (5.00 g, 29.1 mmol), HOBt (4.46 g, 29.1 mmol), EDAC (5.57 g, 29.1 mmol) and triethylamine (4.05 mL, 29.1 mmol) were stirred in DCM (30 mL) for 15 min. *tert*-Butyl piperazine-1-carboxylate (2.71 g, 14.5 mmol) was added and the mixture was stirred at room temperature for 8 h. The reaction was diluted with DCM (10 mL) and washed with 1 N NaOH (5 mL), followed by 1 M citric acid (5 mL). The organic extracts were dried over Na_2SO_4 , filtered, and concentrated to afford an oil that was purified by RP-HPLC. The best fractions were lyophilized to afford material that was neutralized with $NaHCO_3$ (75 mL), and extracted with EtOAc (2 x 200 mL). The organic extracts were dried over Na_2SO_4 , filtered, and concentrated to afford the title compound (1.68 g) as a yellow solid. 1H NMR (DMSO- d_6 , 400 MHz) δ 1.42 (s, 9H), 3.25-3.39 (m, 4H), 3.42-3.48 (m, 2H), 3.49-3.56 (m, 2H), 3.74 (s, 2H), 7.02 (dt, J = 2.7, 8.5 Hz, 1H), 7.18 (dt, J = 2.6, 9.7 Hz, 1H), 7.25-7.33 (m, 1H). Exact mass calculated for $C_{17}H_{22}F_2N_2O_3$: 340.2; Found: LCMS m/z = 341.3 ($M+H^+$).

Step B: Preparation of *tert*-Butyl 4-(2-(2,4-Difluorophenethyl)piperazine-1-carboxylate.

tert-Butyl 4-(2-(2,4-difluorophenyl)acetyl)piperazine-1-carboxylate (1.12 g, 3.30 mmol) was dissolved in THF (8.5 mL) and borane tetrahydrofuran complex (1.0 M, 15.8 mL, 15.8 mmol) was added. The reaction was heated to reflux temperature. The reaction was quenched slowly with methanol (0.4 mL) dropwise. Then, 0.5 M HCl (10.0 mL) was added, and the mixture was extracted with EtOAc (2 x 100 mL). Organic extracts were dried over Na_2SO_4 , filtered, and concentrated to give a residue that was purified by RP-HPLC. The best fractions were added to $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 100 mL). The

organic extracts were dried over Na₂SO₄, filtered, and concentrated to yield the title compound (1.08 g) as a white solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 1.41 (s, 9H), 2.80-2.96 (m, 6H), 3.10-3.03 (m, 2H), 3.50-3.60 (m, 4H), 7.06 (dt, *J* = 2.6, 8.5 Hz, 1H), 7.22 (dt, *J* = 2.6, 9.6 Hz, 1H), 7.38-7.46 (m, 1H). Exact mass calculated for C₁₇H₂₄F₂N₂O₂: 326.2; Found: LCMS *m/z* = 327.1 (M+H⁺).

Step C: Preparation of 1-(2,4-Difluorophenethyl)piperazine.

tert-Butyl 4-(2,4-difluorophenethyl)piperazine-1-carboxylate (0.853 g, 2.61 mmol) was dissolved in 4 M HCl in dioxane (10.0 mL) and stirred for 1 h. The reaction was concentrated to afford the dihydrochloride salt of the title compound (0.718 g) as a pale solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.95-3.75 (m, 12H), 6.03-6.80 (bs, 1H), 7.04-7.12 (m, 1H), 7.24 (dt, *J* = 2.6, 9.6 Hz, 1H), 7.39-7.50 (m, 1H). Exact mass calculated for C₁₂H₁₆F₂N₂: 226.1; Found: LCMS *m/z* = 227.2 (M+H⁺).

Step D: Preparation of {4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone.

To a mixture of 1-methyl-1*H*-indazole-3-carboxylic acid (7.47 mg, 42.4 μmol), HATU (16.1 mg, 42.4 μmol) and *N,N*-diisopropylethylamine (18.5 μl, 106 μmol) in DMA (0.5 ml), a solution of 1-(2,4-difluorophenethyl)piperazine (8.00 mg, 35.4 μmol) in DMA (0.5 ml) was added. The reaction mixture was heated at 120 °C for 20 min under microwave irradiation in a heavy-walled sealed tube. The reaction mixture was concentrated and then purified by RP-HPLC. The best fractions were lyophilized to afford the TFA salt of the title compound (9.20 mg) as a white solid. Exact mass calculated for C₂₁H₂₂F₂N₄O: 384.2; Found: LCMS *m/z* = 385.4 (M+H⁺).

Example 1.36: Preparation of 3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1*H*-indazole-6-carbonitrile (Compound 50).

The title compound was prepared in a similar manner as described in , using 1-(4-fluorophenethyl)piperazine (70 mg, 0.25 mmol) and 6-cyano-1*H*-indazole-3-carboxylic acid (51 mg, 0.27 mmol) as starting materials, to afford the TFA salt (90 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.99-3.16 (m, 3H), 3.16-3.32 (m, 3H), 3.36-3.84 (m, 4H), 4.57-4.91 (m, 1H), 5.01-5.36 (m, 1H), 7.08 (t, *J* = 8.84 Hz, 2H), 7.26-7.32 (m, 2H), 7.51 (dd, *J* = 8.34, 1.26 Hz, 1H), 8.12 (s, 1H), 8.24 (d, *J* = 8.34 Hz, 1H). Exact mass calculated for C₂₁H₂₀FN₅O: 377.2; Found: LCMS *m/z* = 378.1 (M+H⁺).

Example 1.37: Preparation of (6-Bromo-1-methyl-1*H*-indazol-3-yl)-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone (Compound 45).

Step A: Preparation of Intermediate 6-Bromo-1-methyl-1*H*-indazole-3-carboxylic acid.

To potassium hydroxide pellets (1.03 g, 18.4 mmol) in DMSO (10 mL) under a nitrogen atmosphere at room temperature was added 6-bromo-1*H*-indazole-3-carboxylic acid (820 mg, 3.40 mmol). The resulting mixture was stirred at room temperature for 30 min before iodomethane (614 μ L, 9.87 mmol) was added while keeping the reaction temperature near 25 °C. The resulting solution was stirred at room temperature for 45 min before it was poured into ice cold water (80 mL). Glacial acetic acid (1.1 mL) was added and the resulting precipitate was collected by filtration. The filtrate was extracted three times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure to give the crude solid. The crude solid was purified by preparative HPLC using a gradient 0-35 % ACN/H₂O and 1% TFA to afford the TFA salt of the title compound (70 mg) as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 4.13 (s, 3H), 7.45 (dd, *J* = 8.59, 1.52 Hz, 1H), 7.99 (d, *J* = 8.59 Hz, 1H), 8.14 (d, *J* = 1.52 Hz, 1H). Exact mass calculated for C₉H₇BrN₂O₂: 254.0; Found: LCMS *m/z* (%) = 255.4 (M+H⁺ ⁷⁹Br, 100%), 257.4 (M+H⁺ ⁸¹Br, 98%).

Step B: Preparation of {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(6-bromo-1-methyl-1*H*-indazol-3-yl)-methanone.

1-(4-Fluorophenethyl)piperazine (70 mg, 0.25 mmol), 6-bromo-1-methyl-1*H*-indazole-3-carboxylic acid (70 mg, 0.27 mmol), HATU (123 mg, 0.32 mmol), triethylamine (139 μ L, 0.99 mmol) and THF (2 mL) were heated for 20 min at 100 °C under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated under reduced pressure. The resulting oil was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (107 mg) as a solid. ¹H NMR (DMSO-*d*₆, 400 MHz) δ 2.47-2.57 (m, 6H), 2.71-2.78 (m, 2H), 3.66-3.72 (m, 2H), 3.95-4.01 (m, 2H), 4.09 (s, 3H), 7.09 (t, *J* = 8.84 Hz, 2H), 7.24-7.30 (m, 2H), 7.38 (dd, *J* = 8.59, 1.52 Hz, 1H), 7.90 (d, *J* = 8.59 Hz, 1H), 8.10 (d, *J* = 1.52 Hz, 1H). Exact mass calculated for C₂₁H₂₂BrFN₄O: 444.1; Found: LCMS *m/z* (%) = 445.3 (M+H⁺ ⁷⁹Br, 100%), 447.3 (M+H⁺ ⁸¹Br, 98%).

Example 1.38: Preparation of 3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-2-methyl-2*H*-indazole-6-carbonitrile (Compound 35).

The title compound was prepared in a similar manner as described in Example 1.37, using 1-(4-fluorophenethyl)piperazine (70 mg, 0.25 mmol) and 6-cyano-2-methyl-2*H*-indazole-3-carboxylic acid (55 mg, 0.27 mmol) as starting materials, to afford the TFA salt of the title compound (11 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.01-3.11 (m, 4H), 3.21-3.33 (m, 4H), 3.38-3.94 (m, 4H), 4.27 (s, 3H), 7.08 (t, *J* = 8.84 Hz, 2H), 7.26-7.31 (m, 2H), 7.40 (dd, *J* = 8.59, 1.26 Hz, 1H), 7.79 (d, *J* = 8.59 Hz, 1H), 8.25 (s, 1H). Exact mass calculated for C₂₂H₂₂FN₅O: 391.2; Found: LCMS *m/z* = 392.5 (M+H⁺).

Example 1.39: Preparation of (1-Ethyl-1*H*-indazol-3-yl)-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone (Compound 46).

The title compound was prepared in a similar manner as described in Example 1.37, using 1-(4-fluorophenethyl)piperazine (70 mg, 0.25 mmol) and 1-ethyl-1*H*-indazole-3-carboxylic acid (52 mg, 0.27 mmol) as starting materials, to afford the TFA salt of the title compound (39 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 1.50 (t, *J* = 7.33 Hz, 3H), 3.04-3.13 (m, 4H), 3.24-3.30 (m, 2H), 3.42-3.49 (m, 2H), 3.50-3.74 (m, 2H), 4.48 (q, *J* = 7.33 Hz, 2H), 4.61-4.95 (m, 1H), 5.06-5.49 (m, 1H), 7.08 (t, *J* = 8.84 Hz, 2H), 7.25-7.32 (m, 3H), 7.46 (t, *J* = 7.58 Hz, 1H), 7.62 (d, *J* = 8.34 Hz, 1H), 8.09 (d, *J* = 8.34 Hz, 1H). Exact mass calculated for C₂₂H₂₅FN₄O: 380.2; Found: LCMS *m/z* = 381.4 (M+H⁺).

Example 1.40: Preparation of 3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile (Compound 42).

The title compound was prepared in a similar manner as described in Example 1.37, using 1-(4-fluorophenethyl)piperazine (70 mg, 0.25 mmol) and 6-cyano-1-methyl-1*H*-indazole-3-carboxylic acid (55 mg, 0.27 mmol) as starting materials, to afford the TFA salt of the title compound (60 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.47-2.53 (m, 2H), 2.54-2.62 (m, 4H), 2.74-2.81 (m, 2H), 3.72-3.78 (m, 2H), 3.95-4.01 (m, 2H), 4.11 (s, 3H), 7.02 (t, *J* = 8.84 Hz, 2H), 7.23-7.28 (m, 2H), 7.47 (dd, *J* = 8.59, 1.26 Hz, 1H), 8.08 (s, 1H), 8.14 (d, *J* = 8.59 Hz, 1H). Exact mass calculated for C₂₂H₂₂FN₅O: 391.2; Found: LCMS *m/z* = 392.6 (M+H⁺).

Example 1.41: Preparation of (6-Bromo-1-methyl-1*H*-indazol-3-yl)-{4-[2-(2,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone (Compound 43).

The title compound was prepared in a similar manner as described in Example 1.35, Steps A, B and C and Example 1.2, Steps A and B, using 1-(2,4-difluorophenethyl)piperazine (45 mg, 0.2 mmol) and 6-bromo-1-methyl-1*H*-indazole-3-carboxylic acid (56 mg, 0.22 mmol) as starting materials, to afford the TFA salt (27 mg) as a solid. ¹H NMR (CDCl₃, 400 MHz) δ 2.60-2.83 (m, 6H), 2.86-3.00 (m, 2H), 3.87-4.03 (m, 2H), 4.07 (s, 3H), 4.12-4.41 (m, 2H), 6.75-6.85 (m, 2H), 7.16-7.25 (m, 1H), 7.36 (dd, *J* = 8.84, 1.52 Hz, 1H), 7.60 (s, 1H), 8.02 (d, *J* = 8.84 Hz, 1H). Exact mass calculated for C₂₁H₂₁BrF₂N₄O: 462.1; Found: LCMS *m/z* (%) = 463.2 (M+H⁺ ⁷⁹Br, 100%), 465.2 (M+H⁺ ⁸¹Br, 98%).

Example 1.42: Preparation of 3-{4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile (Compound 40).

The title compound was prepared in a similar manner as described in Example 1.41, using 1-(2,4-difluorophenethyl)piperazine (45 mg, 0.2 mmol) and 6-cyano-1-methyl-1*H*-

indazole-3-carboxylic acid (44 mg, 0.22 mmol) as starting materials, to afford the TFA salt (49 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.59-3.01 (m, 2H), 3.08-3.15 (m, 2H), 3.25-3.32 (m, 2H), 3.43-3.87 (m, 4H), 4.14 (s, 3H), 4.53-4.97 (m, 1H), 5.01-5.43 (m, 1H), 6.95 (d, *J* = 8.59 Hz, 1H), 6.97-7.00 (m, 1H), 7.31-7.38 (m, 1H), 7.51 (d, *J* = 8.59 Hz, 1H), 8.11 (s, 1H), 8.22 (d, *J* = 8.59 Hz, 1H). Exact mass calculated for C₂₂H₂₁F₂N₅O: 409.2; Found: LCMS *m/z* = 410.4 (M+H⁺).

Example 1.43: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(6-methoxy-1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 37).

The title compound was prepared in a similar manner as described in Example 1.41, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60 mg, 0.20 mmol) and 6-methoxy-1-methyl-1*H*-indazole-3-carboxylic acid (46 mg, 0.22 mmol) as starting materials, to afford the TFA salt (78 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.39-3.54 (m, 4H), 3.89 (s, 3H), 4.03 (s, 3H), 3.95-4.26 (m, 2H), 4.38-4.66 (m, 2H), 4.72 (s, 2H), 6.89 (dd, *J* = 8.84, 2.02 Hz, 1H), 6.98 (d, *J* = 2.02 Hz, 1H), 7.30 (t, *J* = 8.84 Hz, 2H), 7.93 (d, *J* = 8.84 Hz, 1H), 7.99-8.04 (m, 2H). Exact mass calculated for C₂₂H₂₃FN₄O₃: 410.2; Found: LCMS *m/z* = 411.3 (M+H⁺).

Example 1.44: Preparation of {4-[2,2-Difluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 51).

Step A: Preparation of Intermediate 1-(2,2-Difluoro-2-(4-fluorophenyl)ethyl)piperazine.

A 5 mL vial was charged with piperazine (2.15 g, 25.0 mmol), and the vial was placed into an oil bath at 125 °C. When the piperazine had melted, 1-(2-bromo-1,1-difluoroethyl)-4-fluorobenzene (prepared as described in Schlosser *et al. Tetrahedron* 2004, **60**, 7731-7742) (239 mg, 1.00 mmol) was added, and the mixture was stirred for 3 h. The hot solution was poured into water and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness to give the title compound (73 mg) as a pale yellow oil that was used without further purification. ¹H NMR (CDCl₃, 400 MHz) δ 2.48-2.53 (m, 4H), 2.78-2.82 (m, 4H), 2.91 (t, *J* = 14.0 Hz, 2H), 7.09 (t, *J* = 8.7 Hz, 2H), 7.51 (dd, *J* = 8.7, 5.3 Hz, 2H). Exact mass calculated for C₁₂H₁₅F₃N₂: 244.1; Found: LCMS *m/z* = 245.3 (M+H⁺).

Step B: Preparation of {4-[2,2-Difluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone

EDAC (65.9 mg, 344 μmol) was added to a suspension of 1-methyl-1*H*-indazole-3-carboxylic acid (60.6 mg, 344 μmol) and HOBt (43.9 mg, 287 μmol) in DCM (1 mL), and the mixture was stirred at 20 °C. After 5 min, a clear solution was obtained. The solution was

transferred to a vial containing 1-(2,2-difluoro-2-(4-fluorophenyl)ethyl)piperazine (70 mg, 287 μmol), and the resulting solution was stirred for 4 h. The solution was washed with saturated sodium bicarbonate, dried with sodium sulfate, filtered, and evaporated to dryness. The crude product was purified by flash chromatography on silica gel (2:3 ethyl acetate/hexanes). LCMS showed that the product obtained after flash chromatography contained the HOBt-ester of 1-methyl-1*H*-indazole-3-carboxylic acid as an impurity. The partially purified product was dissolved in DCM, hydrazine hydrate (0.1 mL) was added, and the mixture was stirred at room temperature. After 5 min the mixture was filtered over a short silica column (3:1 ethyl acetate/hexanes), and the filtrate was evaporated to give the title compound (80 mg) as a colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 2.53-2.75 (m, 4H), 2.99 (t, $J = 13.8$ Hz, 2H), 3.71-4.07 (m, 4H), 4.09 (s, 3H), 7.11 (t, $J = 8.6$ Hz, 2H), 7.22-7.28 (m, 1H), 7.38-7.46 (m, 2H), 7.52 (dd, $J = 8.7, 5.3$ Hz, 2H), 8.09 (d, $J = 8.9$ Hz, 1H). Exact mass calculated for $\text{C}_{21}\text{H}_{21}\text{F}_3\text{N}_4\text{O}$: 402.2; Found: LCMS $m/z = 403.4$ ($\text{M}+\text{H}^+$).

Example 1.45: Preparation of {4-[2-Fluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 47).

Step A: Preparation of Intermediate 1-(2-Fluoro-2-(4-fluorophenyl)ethyl)piperazine

A 5 mL vial was charged with piperazine (2.92 g, 3.39 mmol), and the vial was placed into an oil bath at 125 °C. When the piperazine had melted, 1-(2-bromo-1-fluoroethyl)-4-fluorobenzene (prepared as described in Schlosser *et al. Tetrahedron* 2004, **60**, 7731-7742) (300 mg, 1357 μmol) was added, and the mixture was stirred for 3 h. After cooling to room temperature, the crystalline solid was taken up in water and extracted twice with ethyl acetate. The combined organic layers were extracted with 1M HCl, and the aqueous layer was cooled in an ice bath and made strongly alkaline with 6N NaOH. The resulting suspension was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried with sodium sulfate, filtered, and evaporated to dryness to give the title compound (125 mg) as an orange solid that was used without further purification. Exact mass calculated for $\text{C}_{12}\text{H}_{16}\text{F}_2\text{N}_2$: 226.1; Found: LCMS $m/z = 227.4$ ($\text{M}+\text{H}^+$).

Step B: Preparation of {4-[2-Fluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone

EDAC (49.8 mg, 260 μmol) was added to a suspension of 1-methyl-1*H*-indazole-3-carboxylic acid (45.8 mg, 260 μmol) and HOBt (33.2 mg, 217 μmol) in DCM (1 mL), and the mixture was stirred at 20 °C. After 5 min, a clear solution was obtained. The solution was transferred to a vial containing 1-(2-fluoro-2-(4-fluorophenyl)ethyl)piperazine (49 mg, 217 μmol), and the resulting solution was stirred for 4 h. The solution was washed with saturated sodium bicarbonate, dried with sodium sulfate, filtered, and evaporated to dryness. The crude

residue was purified by flash chromatography on silica gel (1% methanol in DCM) to give the title compound (49 mg) as a colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ 2.68 (ddd, *J* = 33.1, 14.3, 2.7 Hz, 1H), 2.59-2.79 (m, 4H), 2.95 (ddd, *J* = 17.3, 14.4, 8.6 Hz, 1H), 3.82-4.20 (m, 4H), 4.11 (s, 3H), 5.67 (ddd, *J* = 48.4, 8.6, 2.6 Hz, 1H), 7.08 (t, *J* = 8.7 Hz, 2H), 7.23-7.29 (m, 1H), 7.34 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.39-7.47 (m, 2H), 8.09-8.13 (m, 1H). Exact mass calculated for C₂₁H₂₂F₂N₄O: 384.2; Found: LCMS *m/z* = 385.4 (M+H⁺).

Example 1.46: Preparation of 1-(4-Fluoro-phenyl)-2-[(*R*)-2-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 44).

Step A: Preparation of Intermediate (*R*)-*tert*-Butyl 4-(2-(4-Fluorophenyl)-2-oxoethyl)-3-methylpiperazine-1-carboxylate.

(*R*)-*tert*-Butyl 3-methylpiperazine-1-carboxylate (1.00 g, 4.99 mmol) was dissolved in DMA (5 mL). 2-Bromo-1-(4-fluorophenyl)ethanone (1.14 g, 5.24 mmol) and triethylamine (1.04 ml, 7.49 mmol) were then added to the solution. The reaction mixture was stirred for 1 h at room temperature. The product was purified by HPLC (5-95% ACN/H₂O) to afford the TFA salt of the title compound (1.94 g) as a solid. Exact mass calculated for C₁₈H₂₅FN₂O₃: 336.2; Found: LCMS *m/z* = 337.5 (M+H⁺).

Step B: Preparation of Intermediate (*R*)-1-(4-Fluorophenyl)-2-(2-methylpiperazin-1-yl)ethanone.

(*R*)-*tert*-Butyl 4-(2-(4-fluorophenyl)-2-oxoethyl)-3-methylpiperazine-1-carboxylate (1.94 g, 4.31 mmol) and 4 M HCl in dioxane (5 mL) were stirred at 45 °C for 20 min. The solvent was removed under reduced pressure to afford the dihydrochloride salt of the title compound (1.33 g). Exact mass calculated for C₁₃H₁₇FN₂O: 236.1; Found: LCMS *m/z* = 237.1 (M+H⁺).

Step C: Preparation of 1-(4-Fluoro-phenyl)-2-[(*R*)-2-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone.

(*R*)-1-(4-Fluorophenyl)-2-(2-methylpiperazin-1-yl)ethanone dihydrochloride (60 mg, 194 μmol), methyl-1*H*-indazole-3-carboxylic acid (44.4 mg, 252 μmol), HATU (95.9 mg, 252 μmol), triethylamine (134 μL, 970 μmol) and THF (3 mL) were heated for 20 min at 100 °C under microwave irradiation in a heavy-walled sealed tube. The solvent was evaporated under reduced pressure. The resulting oil was dissolved in ACN (3 mL) and purified by preparative HPLC to afford the TFA salt of the title compound (3.8 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 1.41 (s, 3H), 2.70-2.88 (s, 4H), 3.36-3.42 (s, 1H), 3.50-3.61 (s, 1H), 3.72-3.81 (s, 1H), 4.13 (s, 3H), 4.62-4.81 (m, 2H), 7.25-7.33 (m, 3H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 8.04-8.11 (m, 3H). Exact mass calculated for C₂₂H₂₃FN₄O₂: 394.2; Found: LCMS *m/z* = 395.5 (M+H⁺).

Example 1.47: Preparation of 2-[4-(5-Fluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 55).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60.0 mg, 0.200 mmol), and 5-fluoro-1*H*-indazole-3-carboxylic acid (43.2 mg, 0.240 mmol) as starting materials, to afford the TFA salt (22.7 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.38-3.50 (s, 4H), 4.00-4.20 (s, 4H), 4.70 (s, 2H), 7.26-7.33 (m, 3H), 7.63-7.69 (m, 1H), 7.68 (td, *J* = 2.2, 9.2 Hz 1H), 8.00-8.05 (m, 2H). Exact mass calculated for C₂₀H₁₈F₂N₄O₂: 384.1; Found: LCMS *m/z* = 385.4 (M+H⁺).

Example 1.48: Preparation of 2-[4-(5,6-Difluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 52).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60.0 mg, 0.200 mmol) and 5,6-difluoro-1*H*-indazole-3-carboxylic acid (47.6 mg, 0.240 mmol) as starting materials, to afford the TFA salt (21.5 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.35-3.43 (s, 4H), 3.79-3.90 (s, 4H), 4.67 (s, 2H), 7.28 (t, *J* = 8.8, 2H), 7.60-7.67 (m, 2H), 7.68 (m, 2H). Exact mass calculated for C₂₀H₁₇F₃N₄O₂: 402.1; Found: LCMS *m/z* = 403.4(M+H⁺).

Example 1.49: Preparation of 2-[4-(5,6-Dichloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone (Compound 48).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60.0 mg, 0.200 mmol) and 5,6-dichloro-1*H*-indazole-3-carboxylic acid (55.4 mg, 0.240 mmol) as starting materials, to afford the TFA salt (13.5 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 3.26-3.41 (s, 4H), 4.0-4.15 (s, 2H), 4.41-4.52 (s, 2H), 4.57 (s, 2H), 7.29 (t, *J* = 8.8, 2H), 7.87 (s, 1H), 8.01-8.05 (m, 2H), 8.26 (s, 1H). Exact mass calculated for C₂₀H₁₇Cl₂FN₄O₂: 434.1; Found: LCMS *m/z* = 435.1 (M+H⁺).

Example 1.50: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(5-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 49).

The title compound was prepared in a similar manner as described in Example 1.2, using 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (60.0 mg, 0.200 mmol) and 5-methyl-1*H*-indazole-3-carboxylic acid (42.3 mg, 0.240 mmol) as starting materials, to afford the TFA salt (20.1 mg) as a solid. ¹H NMR (Acetonitrile-*d*₃, 400 MHz) δ 2.46 (s, 3H), 3.36-3.48 (s, 4H), 4.00-4.20 (s, 2H), 4.35-4.62 (s, 2H), 4.67 (s, 2H), 7.27-7.32 (m, 3H), 7.53

(m, 1H), 7.87 (s, 1H), 8.00-8.04 (m, 2H). Exact mass calculated for $C_{21}H_{21}FN_4O_2$: 380.2; Found: LCMS m/z = 381.1 ($M+H^+$).

Example 1.51: Preparation of {4-[2-(2-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1H-indazol-3-yl)-methanone (Compound 41).

Step A: Preparation of Intermediate (1-methyl-1H-indazol-3-yl)-piperazin-1-yl-methanone.

A mixture of 1-methyl-1H-indazole-3-carboxylic acid (0.500 g, 2.84 mmol), HATU (1.08 g, 2.84 mmol), *N,N*-diisopropylethylamine (545 μ l, 3.12 mmol) and piperazine (733 mg, 8.51 mmol) in DMA (8 mL) was stirred at room temperature overnight. The reaction mixture was purified by preparative HPLC. The fractions containing the title compound were collected, and lyophilized to afford the TFA salt (361 mg) as a white solid. Exact mass calculated for $C_{13}H_{16}N_2O$: 244.1; Found: LCMS m/z = 245.3 ($M+H^+$).

Step B: Preparation of {4-[2-(2-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1H-indazol-3-yl)-methanone

A mixture of (1-methyl-1H-indazol-3-yl)-piperazin-1-yl-methanone (35.8 mg, 0.1 mmol), 1-(2-bromoethyl)-2-chlorobenzene (22.6 μ l, 0.150 mmol) and potassium carbonate (41.5 mg, 0.300 mmol) in DMA (2 mL) was heated at 150 °C for 20 min under microwave irradiation in a heavy walled sealed tube. Potassium carbonate was filtered off. The filtrate was collected and purified by preparative HPLC. The fractions containing the title compound were collected, concentrated and lyophilized to afford the TFA salt (14.2 mg) as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ 3.09-3.81 (m, 8H), 4.14 (s, 3H), 4.62-4.84 (m, 1H), 5.10-5.29 (m, 1H), 6.43-6.65 (m, 2H), 7.28-7.52 (m, 6H), 7.77 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H). Exact mass calculated for $C_{21}H_{23}ClN_4O$: 382.2; Found: LCMS m/z = 383.4 ($M+H^+ ^{35}Cl$, 100%), 385.4 ($M+H^+ ^{37}Cl$, 40%).

Example 1.52: Preparation of {4-[2-(2-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1H-indazol-3-yl)-methanone (Compound 38).

The title compound was prepared in a similar manner as described in Example 1.51, using (1-methyl-1H-indazol-3-yl)-piperazin-1-yl-methanone (35.8 mg, 0.1 mmol) and 1-(2-bromoethyl)-2-fluorobenzene (30.5 mg, 0.150 mmol) as starting materials, to afford the TFA salt (21.1 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS m/z = 367.4 ($M+H^+$).

Example 1.53: Preparation of {4-[2-(3-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1H-indazol-3-yl)-methanone (Compound 57).

The title compound was prepared in a similar manner as described in Example 1.51, using (1-methyl-1*H*-indazol-3-yl)-piperazin-1-yl-methanone (0.025 g, 69.8 μ mol) and 1-(2-bromoethyl)-3-fluorobenzene (21.3 mg, 105 μ mol) as starting materials, to afford the TFA salt (12.7 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}FN_4O$: 366.2; Found: LCMS m/z = 367.3 ($M+H^+$).

Example 1.54: Preparation of {4-[2-(4-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 54).

The title compound was prepared in a similar manner as described in Example 1.51, using (1-methyl-1*H*-indazol-3-yl)-piperazin-1-yl-methanone (25.0 mg, 69.8 μ mol) and 1-(2-bromoethyl)-4-chlorobenzene (15.2 μ l, 105 μ mol) as starting materials, to afford the TFA salt of the title compound (15.6 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}ClN_4O$: 382.2; Found: LCMS m/z = 383.2 ($M+H^+$ ^{35}Cl , 100%), 385.2 ($M+H^+$ ^{37}Cl , 35%).

Example 1.55: Preparation of 1-(4-Chloro-phenyl)-2-[4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 39).

The title compound was prepared in a similar manner as described in Example 1.51, using (1-methyl-1*H*-indazol-3-yl)-piperazin-1-yl-methanone (25.0 mg, 69.8 μ mol) and 2-bromo-1-(4-chlorophenyl)ethanone (24.4 mg, 105 μ mol) as starting materials, to afford the TFA salt (11.8 mg) as a white solid. Exact mass calculated for $C_{21}H_{21}ClN_4O_2$: 396.1; Found: LCMS m/z = 397.2 ($M+H^+$ ^{35}Cl , 100%), 399.2 ($M+H^+$ ^{37}Cl , 35%).

Example 1.56: Preparation of {4-[2-(3-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone (Compound 36).

The title compound was prepared in a similar manner as described in Example 1.51, using (1-methyl-1*H*-indazol-3-yl)-piperazin-1-yl-methanone (25.0 mg, 69.8 μ mol) and 1-(2-bromoethyl)-3-chlorobenzene (23.0 mg, 105 μ mol) as starting materials, to afford the TFA salt (16.9 mg) as a white solid. Exact mass calculated for $C_{21}H_{23}ClN_4O$: 382.2; Found: LCMS m/z = 383.2 ($M+H^+$ ^{35}Cl , 100%), 385.2 ($M+H^+$ ^{37}Cl , 35%).

Example 1.57: Preparation of 1-(4-Fluoro-phenyl)-2-[4-(2-methyl-2*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone (Compound 56).

To a mixture of 1-(4-fluorophenyl)-2-(piperazin-1-yl)ethanone dihydrochloride (59.0 mg, 0.20 mmol) and *N,N*-diisopropylethylamine (105 μ l, 0.60 mmol) in DMA (2 mL), 2-methyl-2*H*-indazole-3-carboxylic acid (38.8 mg, 0.22 mmol) and HATU (83.7 mg, 0.22 mmol) were added. The reaction mixture was stirred at room temperature overnight. The product was purified by preparative HPLC. The fractions containing the title compound were collected, and

lyophilized to afford the TFA salt (61.2 mg) as a white solid. Exact mass calculated for $C_{21}H_{21}FN_4O_2$: 380.2; Found: LCMS m/z = 381.3 ($M+H^+$).

Example 2: Receptor Expression.

5 A. pCMV.

Although a variety of expression vectors are available to those in the art, it is preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the
10 Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

B. Transfection Procedure.

For the IP accumulation assay (Example 6), HEK293 cells were transfected while for
15 the DOI binding assay (Example 3) COS7 cells were transfected. Several protocols well known in the art can be used to transfect cells. The following protocol is representative of the transfection procedures used herein for COS7 or HEK293 cells.

On day one, COS-7 cells or HEK293 cells were plated onto 24-well plates, usually 1×10^5 cells/well or 2×10^5 cells/well respectively. On day two, the cells were transfected by first
20 mixing 0.25 μ g cDNA in 50 μ l serum-free DMEM/well and then 2 μ l lipofectamine in 50 μ l serum-free DMEM/well. The solutions (transfection media) were gently mixed and incubated for 15-30 minutes at room temperature. The cells were washed with 0.5 mL PBS and then 400 μ l of serum free medium was mixed with the transfection media and added to the cells. The cells were then incubated for 3-4 hours at 37 °C/5% CO₂. Then the transfection medium was
25 removed and replaced with 1 mL/well of regular growth medium.

For HEK293 cells, on day one, 13×10^6 cells per 150 mm plate were plated out. On day two, 2 mL of serum OptimemI (Invitrogen Corporation) was added per plate followed by addition of 60 μ L of lipofectamine and 16 μ g of cDNA. Note that lipofectamine must be added to the OptimemI and mixed well before addition of cDNA. While complexes between lipofectamine and
30 the cDNA are forming, medium was carefully aspirated and cells were gently rinsed with 5 mL of OptimemI medium followed by careful aspiration. Then 12 mL of OptimemI was added to each plate and 2 mL of transfection solution was added followed by a 5 hour incubation at 37 °C in a 5% CO₂ incubator. Plates were then carefully aspirated and 25 mL of Complete Media were added to each plate and cells were then incubated until used.

35

Example 3: Binding Assays.

Compounds of the invention were tested for their ability to bind to a 5-HT_{2A} serotonin receptor clone membrane preparation using a radioligand binding assay. Briefly, COS cells were transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:24).

A. Preparation of Crude Membrane Preparations for Radioligand Binding Assays.

COS7 cells transfected with recombinant human 5-HT_{2A} serotonin receptors were cultured for 48 h post transfection, collected, washed with ice-cold phosphate buffered saline, pH 7.4 (PBS), and then centrifuged at 48,000 g for 20 min at 4 °C. The cell pellet was then resuspended in wash buffer containing 20 mM HEPES pH 7.4 and 0.1 mM EDTA, homogenized on ice using a Brinkman polytron, and recentrifuged at 48,000 g for 20 min at 4 °C. The resultant pellet was then resuspended in 20 mM HEPES, pH 7.4, homogenized on ice, and centrifuged (48,000 g for 20 min at 4 °C). Crude membrane pellets were stored at -80 °C until used for radioligand binding assays.

B. [¹²⁵I]DOI Radioligand Binding Assay.

Radioligand binding assays for human 5-HT_{2A} serotonin receptor was conducted using the 5-HT₂ agonist [¹²⁵I]DOI as radioligand. To define nonspecific binding, 10 μM DOI was used for all assays. For competitive binding studies, 0.5 nM [¹²⁵I]DOI was used and compounds were assayed over a range of 0.01 nM to 10 μM. Assays were conducted in a total volume of 200 μl in 96-well Perkin Elmer GF/C filter plates in assay buffer (50 mM Tris-HCl, pH 7.4, 0.5 mM EDTA, 5 mM MgCl₂, and 10 μM pargyline). Assay incubations were performed for 60 min at room temperature and were terminated by rapid filtration under vacuum pressure of the reaction mixture over Whatman GF/C glass fiber filters presoaked in 0.5% PEI using a Brandell cell harvester. Filters were then washed several times with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4). Plates were then dried at room temperature and counted in a Wallac MicroBeta scintillation counter. Certain compounds of the present invention and their corresponding activity values are shown in TABLE B.

TABLE B

Compound No.	IC ₅₀ DOI Binding Assay (nM)
18	2
7	2.3
6	597
4	12
51	.56

Certain other compounds of the invention had activity values ranging from about 10 μ M to about 0.4 nM in this assay.

Example 4: 5-HT_{2A} Receptor Binding.

5 Animals:

Animals (Sprague-Dawley rats) are sacrificed and brains are rapidly dissected and frozen in isopentane maintained at -42 °C. Horizontal sections are prepared on a cryostat and maintained at -20 °C.

LSD Displacement Protocol:

10 Lysergic acid diethylamide (LSD) is a potent 5-HT_{2A} serotonin receptor and dopamine D₂ receptor ligand. An indication of the selectivity of compounds for either or both of these receptors involves displacement of radiolabeled-bound LSD from pre-treated brain sections. For these studies, radiolabeled ¹²⁵I-LSD (NEN Life Sciences, Boston, MA; Catalog number NEX-199) can be utilized; spiperone (RBI, Natick, MA; Catalog number s-128) a 5-HT_{2A}
15 receptor and dopamine D₂ receptor antagonist, can also utilized. Buffer consists of 50 nanomolar TRIS-HCl, pH 7.4.

Brain sections are incubated in (a) Buffer plus 1 nanomolar ¹²⁵I-LSD; (b) Buffer plus 1 nanomolar ¹²⁵I-LSD and 1 micromolar spiperone; or Buffer plus 1 nanomolar ¹²⁵I-LSD and 1 micromolar compound of interest for 30 min at room temperature. Sections are then washed 2
20 x 10 min at 4 °C in Buffer, followed by 20 s in distilled H₂O. Slides are then air-dried.

After drying, sections are apposed to x-ray film (Kodak Hyperfilm) and exposed for 4 days.

Example 5: *In vitro* Human Platelet Aggregation Assays.

25 Compounds of the invention were tested for their ability to aggregate human platelets. Aggregation assays were performed using a Chrono-Log Optical aggregometer model 410. Human blood (~100 mL) was collected from human donors into glass Vacutainers containing 3.8% sodium citrate (light blue tops) at room temperature. Platelet rich plasma (PRP) was isolated *via* centrifugation at 100 g for 15 min at room temperature. After removal of the
30 aqueous PRP layer, the platelet poor plasma (PPP) was prepared *via* high speed centrifugation at 2400 g for 20 min. Platelets were counted and their concentration was set to 250,000 cells/ μ L by dilution with PPP. Aggregation assays were conducted according to the manufacturer's specifications. Briefly, a suspension of 450 μ L PRP was stirred in a glass cuvette (1200 rpm) and, after baseline was established, 1 μ M ADP followed by either saline or
35 1 μ M 5-HT and compound of interest (at desired concentrations) were added and the aggregation response recorded. The concentration of ADP used causes approximately 10-20% of maximal aggregation. The 5-HT concentration corresponded to the concentration which

produced maximal potentiation. Percent inhibition of aggregation was calculated from the maximum decrease in optical density of the controls and of the samples containing inhibitors. Only the synergistic effect was assessed. Certain compounds of the invention had activity values ranging from about 80 μ M to about 15 nM in this assay. Other compounds of the invention had activity values ranging from about 8 μ M to about 15 nM in this assay.

Example 6: Inositol Phosphate (IP) Accumulation Assays.

A. 5-HT_{2A} Receptor.

Compounds of the invention can be tested for their ability to activate a 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, HEK293 cells are transiently transfected with a pCMV expression vector containing a human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:24). An IP accumulation assay can be performed as described below.

B. Constitutively Active 5-HT_{2A} Receptor.

Compounds of the invention can be tested for their ability to inhibit a constitutively active 5-HT_{2A} receptor clone using an IP accumulation assay. Briefly, 293 cells are transiently transfected with a pCMV expression vector containing a constitutively active human 5-HT_{2A} receptor (for the sequence of the receptor see U.S. Patent No. 6,541,209, SEQ ID NO:30). The constitutively active human 5-HT_{2A} receptor contained the human 5-HT_{2A} receptor described in part A except that intracellular loop 3 (IC3) and the cytoplasmic tail are replaced by the corresponding human INI 5-HT_{2C} cDNA. An IP accumulation assay can be performed as described below.

C. IP Accumulation Assay Protocol.

On the day after transfections, medium is removed and the cells are washed with 5 mL PBS followed by careful aspiration. Cells are then trypsinized with 2 mL of 0.05% trypsin for 20-30 s followed by addition of 10 mL of warmed medium, gently titrated to dissociate cells, and an additional 13 mL of warmed medium was gently added. Cells are then counted and 55,000 cells are added to 96-well sterile poly-D-lysine treated plates. Cells are allowed to attach over a six hour incubation at 37 °C in a 5% CO₂ incubator. Medium is then carefully aspirated and 100 μ L of warm inositol-free medium plus 0.5 μ Ci ³H-inositol are added to each well and the plates are incubated for 18-20 hours at 37 °C in a 5% CO₂ incubator.

On the next day, medium is carefully aspirated and then 0.1 mL of assay medium is added containing inositol-free/serum free medium, 10 μ M pargyline, 10 mM lithium chloride, and test compound at indicated concentrations. The plates are then incubated for three hours at 37 °C and then wells are carefully aspirated. Then 200 μ L of ice-cold 0.1M formic acid is added to each well. Plates can then be frozen at this point at -80 °C until further processed. Frozen plates are then thawed over the course of 1 h, and the contents of the wells

(approximately 220 μ L) are placed over 400 μ L of washed ion-exchange resin (AG 1-X8) contained in a Multi Screen Filtration plate and incubated for 10 min followed by filtration under reduced pressure. Resin is then washed with 9 x 200 μ L of water and then tritiated inositol phosphates (IP, IP2, and IP3) are eluted into a collecting plate by the addition of 200 μ L of 1 M ammonium formate and an additional 10 min incubation. The eluent is then transferred to 20 mL scintillation vials, 8 mL of SuperMix or Hi-Safe scintillation cocktail is added, and vials are counted for 0.5-1 min in a Wallac 1414 scintillation counter.

Example 7: Efficacy of Compounds of the Invention in the Attenuation of DOI-induced Hypolocomotion in Rats.

In this example, compounds of the invention were tested for inverse agonist activity by determining whether these compounds could attenuate DOI-induced hypolocomotion in rats in a novel environment. DOI is a potent 5-HT_{2A/2C} receptor agonist that crosses the blood-brain barrier. The standard protocol used is described briefly below.

Animals:

Male Sprague-Dawley rats weighing between 200-350g were used for all tests. Rats were housed three to four per cage.

Compounds:

(R)-DOI HCl (C₁₁H₁₆INO₂·HCl) was obtained from Sigma-Aldrich, and was dissolved in 0.9% saline. Compounds of the invention were synthesized at Arena Pharmaceuticals Inc., San Diego, CA, and were dissolved in 100% PEG400. DOI was injected s.c. in a volume of 1 mL/kg, while compounds of the invention were administered p.o. in a volume of 1 mL/kg.

Procedure:

The "Motor Monitor" (Hamilton-Kinder, Poway, CA) was used for all activity measurement. This apparatus recorded rears using infrared photobeams.

Locomotor activity testing was conducted during the light cycle between 9:00 a.m. and 4:00 p.m. Animals were allowed 30 min acclimation to the testing room before testing began.

In determining the effects of compounds of the invention on DOI-induced hypoactivity, animals were first injected with vehicle or the compound of the invention (1-10 mg/kg) in their home cages. Twenty five minutes later, saline or DOI (1 mg/kg salt) was injected. Ten minutes after DOI administration, animals were placed into the activity apparatus and rearing activity was measured for 10 min.

Statistics and Results:

Results (total rears over 10 minutes) were analyzed by t-test. P<0.05 was considered significant. As shown in Figure 6, Compound 8 attenuated DOI-induced hypolocomotion in rats. In addition, as shown in Figure 7, Compound 17 also attenuated DOI-induced hypolocomotion in rats.

Example 8: Serotonin 5-HT_{2A} Receptor Occupancy Studies in Monkey.

In this example, the 5-HT_{2A} receptor occupancy of a compound of the invention can be measured. The study can be carried out in rhesus monkeys using PET and ¹⁸F-altanserin.

5 Radioligand:

The PET radioligand used for the occupancy studies is ¹⁸F-altanserin. Radiosynthesis of ¹⁸F-altanserin is achieved in high specific activities and is suitable for radiolabeling 5-HT_{2A} receptors *in vivo* (see Staley *et al.*, *Nucl. Med. Biol.*, 28:271-279 (2001) and references cited within). Quality control issues (chemical and radiochemical purity, specific activity, stability
10 etc) and appropriate binding of the radioligand are verified in rat brain slices prior to use in PET experiments.

Drug Doses and Formulations:

Briefly, the radiopharmaceutical is dissolved in sterile 0.9% saline, pH approx 6-7. The compounds of the invention are dissolved in 60% PEG 400 - 40% sterile saline on the
15 same day of the PET experiment.

Serotonin 5-HT_{2A} occupancy studies in humans have been reported for M100,907 (Grunder *et al.*, *Neuropsychopharmacology*, 17:175-185 (1997), and Talvik-Lofti *et al.*, *Psychopharmacology*, 148:400-403 (2000)). High occupancies of the 5-HT_{2A} receptors have been reported for various oral doses (doses studied ranged from 6 to 20 mg). For example, an
20 occupancy of >90% was reported for a dose of 20 mg (Talvik-Lofti *et al.*, *supra*), which translates to approx. 0.28 mg/kg. It may therefore be anticipated that an i.v. dose of 0.1 to 0.2 mg/kg of M100,907 is likely to provide high receptor occupancy. A 0.5 mg/kg dose of a compound of the invention can be used in these studies.

PET Experiments:

25 The monkey is anesthetized by using ketamine (10 mg/kg) and is maintained using 0.7 to 1.25% isoflurane. Typically, the monkey has two i.v. lines, one on each arm. One i.v. line is used to administer the radioligand, while the other line is used to draw blood samples for pharmacokinetic data of the radioligand as well as the cold drugs. Generally, rapid blood samples are taken as the radioligand is administered which then taper out by the end of the
30 scan. A volume of approximately 1 mL of blood is taken per time point, which is spun down, and a portion of the plasma is counted for radioactivity in the blood.

An initial control study is carried out in order to measure baseline receptor densities. PET scans on the monkey are separated by at least two weeks. Unlabeled Compound of the invention is administered intravenously, dissolved in 80% PEG 400:40% sterile saline.

35 PET Data Analysis:

PET data are analyzed by using cerebellum as the reference region and using the distribution volume region (DVR) method. This method has been applied for the analysis of

¹⁸F-altanserin PET data in nonhuman primate and human studies (Smith *et al.*, Synapse, 30:380-392 (1998).

Example 9: The Effect of Compounds of the Invention and Zolpidem on Delta Power in Rats.

In this example, the effect of compounds of the invention on sleep and wakefulness can be compared to the reference drug zolpidem. Drugs are administered during the middle of the light period (inactivity period).

Briefly, compounds of the invention are tested for their effects on sleep parameters and are compared to zolpidem (5.0 mg/kg, Sigma, St. Louis, MO) and vehicle control (80% Tween 80, Sigma, St. Louis, MO). A repeated measures design is employed in which each rat is to receive seven separate dosings via oral gavage. The first and seventh dosings are vehicle and the second through sixth are the test compounds and zolpidem given in counter-balanced order. Since all dosings are administered while the rats are connected to the recording apparatus, 60% CO₂/40% O₂ gas is employed for light sedation during the oral gavage process. Rats are fully recovered within 60 seconds following the procedure. A minimum of three days elapses between dosings. In order to test the effect of the compounds on sleep consolidation, dosing occurs during the middle of the rats' normal inactive period (6 h following lights on). Dosing typically occurs between 13:15 and 13:45 using a 24 hour notation. All dosing solutions are made fresh on the day of dosing. Following each dosing, animals are continuously recorded until lights out the following day (~30 h).

Animal Recording and Surgical Procedures:

Animals are housed in a temperature controlled recording room under a 12/12 light/dark cycle (lights on at 7:00 am) and have food and water available *ad libitum*. Room temperature (24 ± 2 °C), humidity (50 ± 20% relative humidity) and lighting conditions are monitored continuously *via* computer. Drugs are administered *via* oral gavage as described above, with a minimum of three days between dosings. Animals are inspected daily in accordance with NIH guidelines.

Eight male Wistar rats (300 ± 25 g; Charles River, Wilmington, MA) are prepared with chronic recording implants for continuous electroencephalograph (EEG) and electromyograph (EMG) recordings. Under isoflurane anesthesia (1-4%), the fur is shaved from the top of the skull and the skin was disinfected with Betadine and alcohol. A dorsal midline incision is made, the temporalis muscle retracted, and the skull cauterized and thoroughly cleaned with a 2% hydrogen peroxide solution. Stainless steel screws (#000) are implanted into the skull and served as epidural electrodes. EEG electrodes are positioned bilaterally at +2.0 mm AP from bregma and 2.0 mm ML and at -6.0 mm AP and 3.0 mm ML. Multi-stranded twisted stainless steel wire electrodes are sutured bilaterally in the neck muscles for recording of the EMG.

EMG and EEG electrodes are soldered to a head plug connector that was affixed to the skull with dental acrylic. Incisions are closed with suture (silk 4-0) and antibiotics administered topically. Pain is relieved by a long-lasting analgesic (buprenorphine) administered intramuscularly once post-operatively. Post-surgery, each animal is placed in a clean cage and observed until it is recovered. Animals are permitted a minimum of one week post-operative recovery before study.

For sleep recordings, animals are connected via a cable and a counter-balanced commutator to a Neurodata model 15 data collection system (Grass-Telefactor, West Warwick, RI). The animals are allowed an acclimation period of at least 48 hours before the start of the experiment and are connected to the recording apparatus continuously throughout the experimental period except to replace damaged cables. The amplified EEG and EMG signals are digitized and stored on a computer using SleepSign software (Kissei Comtec, Irvine, CA).

Data Analysis:

EEG and EMG data are scored visually in 10 s epochs for waking (W), REMS and NREMS. Scored data are analyzed and expressed as time spent in each state per half hour. Sleep bout length and number of bouts for each state are calculated in hourly bins. A "bout" consists of a minimum of two consecutive epochs of a given state. EEG delta power (0.5-3.5 Hz) within NREMS is also analyzed in hourly bins. The EEG spectra during NREMS are obtained offline with a fast Fourier transform algorithm on all epochs without artifact. The delta power is normalized to the average delta power in NREMS between 23:00 and 1:00, a time when delta power is normally lowest.

Data are analyzed using repeated measures ANOVA. Light phase and dark phase data are analyzed separately. Both the treatment effect within each rat and the time by treatment effect within each rat is analyzed. Since two comparisons are made, a minimum value of $P < 0.025$ is required for *post hoc* analysis. When statistical significance is found from the ANOVAs, t-tests are performed comparing all compounds to vehicle and the test compounds to zolpidem.

Example 10: Efficacy of Compounds of the Invention in the Inhibition of JC Virus Infection of Human Glial Cells.

A compound of the invention can be shown to inhibit JC virus infection of human glial cells using the *in vitro* model of Elphick *et al.* [*Science* (2004) 306:1380-1383], essentially as described briefly here.

Cells and JC Virus

The human glial cell line SVG (or a suitable subclone thereof, such as SVG-A) is used for these experiments. SVG is a human glial cell line established by transformation of human fetal glial cells by an origin defective SV40 mutant [Major *et al.*, *Proc. Natl. Acad. Sci. USA*

(1985) 82:1257-1261]. SVG cells are cultured in Eagle's minimum essential medium (Mediatech Inc., Herndon, VA) supplemented with 10% heat-inactivated fetal bovine serum, and kept in a humidified 37 °C 5% CO₂ incubator.

The Mad-1/SVEΔ strain of JC virus [Vacante *et al.*, *Virology* (1989) 170:353-361] is used for these experiments. While the host range of JC virus is typically limited to growth in human fetal glial cells, the host range of Mad-1/SVEΔ extends to human kidney and monkey cell types. Mad-1/SVEΔ is propagated in HEK cells. Virus titer is measured by hemagglutination of human type O erythrocytes.

Assay for Inhibition of JC Virus Infection

SVG cells growing on coverslips are pre-incubated at 37 °C for 45 min with or without the compound of the invention diluted in media containing 2% FCS. By way of illustration and not limitation, the compound of the invention is used at a concentration of about 1 nM to about 100 μM, at a concentration of about 10 nM to about 100 μM, at a concentration of about 1nM to about 10μM, or at a concentration of about 10nM to about 10μM.

JC virus (Mad-1/SVEΔ) is then added at an MOI of 1.0 and the cells are incubated for 1 h at 37 °C in the continued presence of the compound of the invention. The cells are then washed 3 x in PBS and fed with growth media containing the compound of the invention. At 72 h post-infection, V antigen positive cells are scored by indirect immunofluorescence (see below). Controls include the addition of the compound of the invention at 24 and 48 h post-infection. The percentage of infected cells in untreated cultures is set at 100%.

Indirect Immunofluorescence

For indirect immunofluorescence analysis of V antigen expression, SVG cells growing on coverslips are fixed in ice cold acetone. To detect V antigen expression, the cells are then incubated for 30 min at 37 °C with a 1:10 dilution of hybridoma supernatant from PAB597.

The PAB597 hybridoma produces a monoclonal antibody against the SV40 capsid protein VP1 which has been shown to cross-react with JC virus VP1. The cells are then washed and incubated with goat anti-mouse Alexa Fluor 488 secondary antibody for an additional 30 min. After a final wash, the cells are counterstained with 0.05% Evan's blue, mounted onto glass slides using 90% glycerol in PBS and visualized on Nikon E800 epifluorescent scope. Images are captured using a Hamamatsu digital camera and analyzed using Improvision software.

Example 11: In Vitro Dog Platelet Aggregation Assays.

Approximately 50 mL of blood is pooled from 3 male beagles. The protocol for analyzing the effects of compounds on platelet aggregation are identical to those used for human platelets (see Example 5, *supra*) except 5 μM ADP and 2 μM 5-HT were used to stimulate amplification of platelet aggregation.

Example 12: Ex-Vivo Dog Whole Blood Aggregation.

One hour following p.o. dosing with a test compound whole blood is collected from male beagle dogs in a 5 mL Vacutainer with exogenous heparin (5 U/mL) added to the Vacutainer. Aggregation studies are evaluated by using a whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 μ L) is added to saline (600 μ L) with constant stirring and activated with 5 μ g of Collagen (Chronolog Corp.). The serotonin response is obtained by adding 5-HT (Sigma) to a final concentration of 2.5 μ M.

Results: Selected compounds are tested for anti-platelet aggregation activity after single bolus oral dosing. The dose that affords maximal inhibition of 5-HT amplified platelet aggregation is identified and used for comparison.

Example 13: Rat *In Vivo* Thrombosis, Bleeding, Aggregation, PK Assay.

Thrombosis formation and bleeding time: This model concomitantly measures thrombus formation, bleeding time, platelet aggregation and drug exposure in a single live dosed rat. Test compounds are administered to male rats (weighing 250-350 g) via p.o. injection at varying concentrations depending on compound potency ranging from 1 mg/kg-100 mg/kg. Animals are then anesthetized using Nembutal approximately 30 min post administration. Once the animal is fully anesthetized using approved surgical techniques the animal's right femoral artery is isolated in 2 different sections approximately 4-6 mm in length, one area for probe placement and one for ferric chloride patch positioning. The artery is then allowed to stabilize to allow recovery from the surgery. During stabilization the animal is then intubated and placed on a ventilator (Harvard Apparatus, Inc.) at 75 strokes/min with a volume of 2.5 cm³. Following intubation and after stabilization a micro arterial probe (Transonic Systems, Inc.) is then placed on the distal isolated femoral artery. Once the probe is in place the flow is monitored using a Powerlab recording system (AD Instruments) to monitor rate of pulsatile flow. A small piece of filter paper soaked in 30% ferric chloride is placed on the area of the artery upstream of the probe for 10 min. After 5 min of ferric chloride patch placement the last 3 mm of the rat's tail is removed. The tail is then placed in a saline filled glass vial at 37 °C and the time it took for bleeding to stop is recorded. After the ferric chloride patch is removed the flow is recorded until the artery is occluded and the time to occlusion is recorded.

Whole Blood Aggregation and PK: Following measurement of bleeding and time to occlusion 5 mL of blood is obtained for *ex vivo* aggregation analysis by cardiac puncture in heparin (5U/mL). An additional 500 μ L of blood is collected in a separate Vacutainer for PK analysis (plasma drug concentration). *Ex vivo* aggregation studies are evaluated by using a whole blood Aggregometer (Chronolog Corp.). Briefly, whole blood (400 μ L) is added to saline (600 μ L) with constant stirring and activated with 2.55 μ g of Collagen (Chronolog Corp.). The serotonin response is obtained by adding 5-HT (Sigma) to a final concentration of 2.5 μ M.

Results: Test compounds or reference compounds with acceptable levels of binding to rat 5-HT_{2A} serotonin receptors are evaluated for effects of thrombus formation, bleeding and platelet activity in a single model. This allows for the most accurate demonstration of separation of the test compound effects on platelet mediated thrombus formation from effects on bleeding.

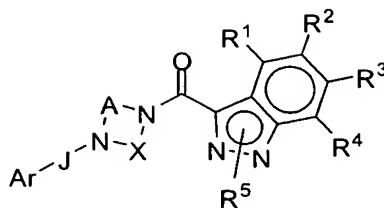
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Those skilled in the art will recognize that various modifications, additions, substitutions, and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but are not limited to, printed

10 publications, and provisional and regular patent applications, are incorporated herein by reference in their entirety.

What is claimed is:

1. A compound of Formula (Ia):



(Ia)

- 5 or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R¹, R², R³ and R⁴ are each independently selected from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl, cyano, C₁-C₆ haloalkoxy, halogen and heteroaryl; and wherein C₁-C₆ alkyl, aryl and heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C₁-C₆ acyl, C₁-C₆ acyloxy, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ alkylureyl, C₁-C₆ alkylamino, C₂-C₆ alkynyl, amino, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylamino, C₂-C₆ dialkylcarboxamide, C₂-C₆ dialkylsulfonamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, C₁-C₆ haloalkylthio, halogen, hydroxyl, nitro, sulfonamide and thiol;

R⁵ is selected from the group consisting of H, C₁-C₆ acyl, C₁-C₆ alkyl, arylcarbonyl, arylsulfonyl, C₃-C₇ cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

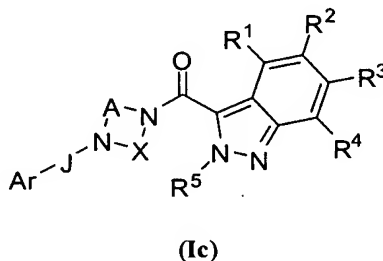
A and X are each -CH₂CH₂-, and each optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C₁-C₄ alkoxy, C₁-C₃ alkyl, carboxy, cyano, C₁-C₃ haloalkyl, halogen, hydroxyl and oxo;

J is -CH₂CH₂- optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of C₁-C₄ alkoxy, C₁-C₃ alkyl, carboxy, cyano, C₁-C₃ haloalkyl, halogen, hydroxyl and oxo; and

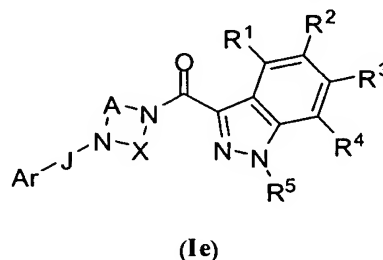
Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of C₁-C₆ acyl, C₁-C₆ acyloxy, C₂-C₆ alkenyl, C₁-C₆ alkoxy, C₁-C₆ alkyl, C₁-C₆ alkylcarboxamide, C₁-C₆ alkylsulfonamide, C₁-C₆ alkylsulfinyl, C₁-C₆ alkylsulfonyl, C₁-C₆ alkylthio, C₁-C₆ alkylureyl, C₁-C₆ alkylamino, C₂-C₆ alkynyl, amino, carbo-C₁-C₆-alkoxy, carboxamide, carboxy, cyano, C₃-C₇ cycloalkyl, C₂-C₆ dialkylamino, C₂-C₆ dialkylcarboxamide, C₂-

C₆ dialkylsulfonamide, C₁-C₆ haloalkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkylsulfinyl, C₁-C₆ haloalkylsulfonyl, C₁-C₆ haloalkylthio, halogen, hydroxyl, nitro, sulfonamide and thiol.

- 5 2. The compound according to claim 1, having Formula (Ic):



3. The compound according to claim 1, having Formula (Ie):



10

4. The compound according to any one of claims 1 to 3, wherein each R¹, R², R³ and R⁴ is selected independently from the group consisting of H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl, cyano, C₁-C₆ haloalkoxy, halogen and heteroaryl; each optionally substituted with C₁-C₆ alkyl.

15

5. The compound according to any one of claims 1 to 3, wherein each R¹, R², R³ and R⁴ is selected independently from the group consisting of H, methoxy, methyl, 2-methylphenyl, cyano, trifluoromethoxy, fluoro, chloro and bromo.

20

6. The compound according to any one of claims 1 to 3, wherein R¹ is H or C₁-C₆ alkyl; R² is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, aryl or halogen, and aryl is optionally substituted with C₁-C₆ alkyl; R³ is H, C₁-C₆ alkoxy, C₁-C₆ alkyl, cyano, C₁-C₆ haloalkoxy or halogen; and R⁴ is H or C₁-C₆ alkoxy.

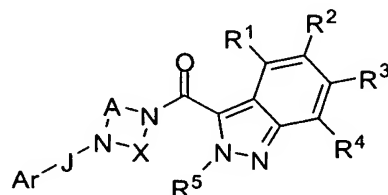
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7. The compound according to any one of claims 1 to 3, wherein R¹ is H or methyl; R² is H, methoxy, methyl, 2-methyl-phenyl, fluoro, chloro or bromo; R³ is H, methoxy, methyl, cyano, trifluoromethoxy, fluoro, chloro or bromo; and R⁴ is H or methoxy.

8. The compound according to any one of claims 1 to 7, wherein R⁵ is selected from the group consisting of H, C₁-C₆ alkyl, arylcarbonyl, arylsulfonyl, C₃-C₇ cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens.
9. The compound according to any one of claims 1 to 7, wherein R⁵ is selected from the group consisting of H, 1*H*-indazole-3-carbonyl, 4-fluorobenzoyl, methyl, ethyl, *n*-propyl, isopropyl, benzenesulfonyl and cyclopentyl.
10. The compound according to any one of claims 1 to 9, wherein A and X are each -CH₂CH₂-, and each optionally substituted with C₁-C₃ alkyl.
11. The compound according to any one of claims 1 to 9, wherein A and X are each -CH₂CH₂-, and each optionally substituted with methyl.
12. The compound according to any one of claims 1 to 9, wherein A and X are each independently -CH₂CH₂- or -CH(CH₃)CH₂-.
13. The compound according to any one of claims 1 to 12, wherein J is -CH₂CH₂- optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo.
14. The compound according to any one of claims 1 to 12, wherein J is -CH₂CH₂- optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of fluoro and oxo.
15. The compound according to any one of claims 1 to 12, wherein J is -CH₂CH₂-, -C=OCH₂-, -CHFCH₂- or -CF₂CH₂-.
16. The compound according to any one of claims 1 to 15, wherein Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.
17. The compound according to any one of claims 1 to 15, wherein Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 substituents selected independently from the group consisting of fluoro and chloro.

18. The compound according to any one of claims 1 to 15, wherein Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.

- 5 19. The compound according to claim 1, having Formula (Ic):



(Ic)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R^1 is H or C_1 - C_6 alkyl;

10 R^2 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, aryl or halogen; wherein aryl is optionally substituted with C_1 - C_6 alkyl;

R^3 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_1 - C_6 haloalkoxy or halogen;

R^4 is H or C_1 - C_6 alkoxy;

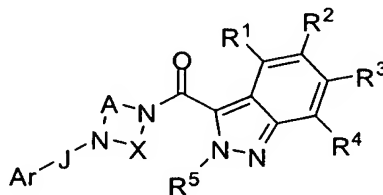
15 R^5 is H, C_1 - C_6 alkyl, arylcarbonyl, arylsulfonyl, C_3 - C_7 cycloalkyl or heteroarylcarbonyl; wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

A and X are each independently $-CH_2CH_2-$, and each optionally substituted with C_1 - C_3 alkyl;

J is $-CH_2CH_2-$ optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo; and

20 Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.

20. The compound according to claim 1, having Formula (Ic):



(Ic)

25 or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R^1 is H or methyl;

R^2 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, aryl or halogen; wherein aryl is optionally substituted with C_1 - C_6 alkyl;

R^3 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_1 - C_6 haloalkoxy or halogen;

R^4 is H or C_1 - C_6 alkoxy;

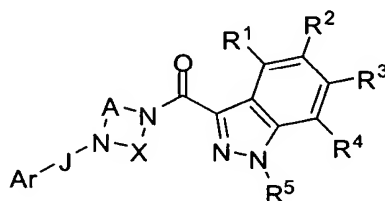
5 R^5 is H, C_1 - C_6 alkyl, arylcarbonyl, arylsulfonyl, C_3 - C_7 cycloalkyl or heteroarylcarbonyl; wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

A and X are each independently $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}(\text{CH}_3)\text{CH}_2-$;

J is $-\text{CH}_2\text{CH}_2-$, $-\text{C}=\text{OCH}_2-$, $-\text{CHFCH}_2-$ or $-\text{CF}_2\text{CH}_2-$; and

10 Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.

21. The compound according to claim 1, having Formula (Ie):



(Ie)

15 or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R^1 is H or C_1 - C_6 alkyl;

R^2 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, aryl or halogen, and aryl is optionally substituted with C_1 - C_6 alkyl;

R^3 is H, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, cyano, C_1 - C_6 haloalkoxy or halogen;

20 R^4 is H or C_1 - C_6 alkoxy;

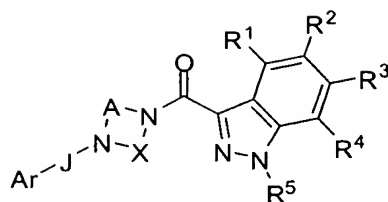
R^5 is selected from the group consisting of H, C_1 - C_6 acyl, C_1 - C_6 alkyl, arylcarbonyl, arylsulfonyl, C_3 - C_7 cycloalkyl and heteroarylcarbonyl; and wherein arylcarbonyl and heteroarylcarbonyl are each optionally substituted with 1, 2, 3, 4 or 5 halogens;

25 A and X are each independently $-\text{CH}_2\text{CH}_2-$, and each optionally substituted with C_1 - C_3 alkyl;

J is $-\text{CH}_2\text{CH}_2-$ optionally substituted with 1, 2, 3 or 4 substituents selected independently from the group consisting of halogen and oxo; and

30 Ar is aryl or heteroaryl each optionally substituted with 1, 2, 3, 4 or 5 halogen atoms.

22. The compound according to claim 1, having Formula (Ie):



(Ie)

or a pharmaceutically acceptable salt, solvate or hydrate thereof; wherein:

R¹ is H or methyl;

R² is H, methoxy, methyl, 2-methyl-phenyl, fluoro, chloro or bromo;

5 R³ is H, methoxy, methyl, cyano, trifluoromethoxy, fluoro, chloro or bromo;

R⁴ is H or methoxy;

R⁵ is H, 1*H*-indazole-3-carbonyl, 4-fluorobenzoyl, methyl, ethyl, *n*-propyl, isopropyl, benzenesulfonyl or cyclopropyl;

A and X are each independently -CH₂CH₂- or -CH(CH₃)CH₂-;

10 J is -CH₂CH₂-, -C=OCH₂-, -CHFCH₂- or -CF₂CH₂-; and

Ar is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl or 4-chlorophenyl.

23. The compound according to claim 1 selected from the group consisting of:

15 1-(4-Fluoro-phenyl)-2-[(*S*)-4-(1*H*-indazole-3-carbonyl)-2-methyl-piperazin-1-yl]-ethanone;

3-{4-[2-(4-Fluoro-phenyl)-2-oxo-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile;

2-[4-(5-Chloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

20 1-(4-Fluoro-phenyl)-2-[4-(1-isopropyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;

1-(4-Fluoro-phenyl)-2-[(*S*)-2-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;

25 2-[4-(6-Bromo-2-methyl-2*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

2-[4-(6-Fluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

2-[4-(1-Ethyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

2-[4-(1-Cyclopentyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

30 2-[4-(5,6-Dimethoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

- 1-(4-Fluoro-phenyl)-2-[4-(7-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 1-(4-Fluoro-phenyl)-2-{4-[1-(1*H*-indazole-3-carbonyl)-1*H*-indazole-3-carbonyl]-piperazin-1-yl}-ethanone;
- 5 2-[4-(6-Chloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
- 1-(4-Fluoro-phenyl)-2-[4-(5-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 1-(4-Fluoro-phenyl)-2-[4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- {(S)-4-[2-(4-Fluoro-phenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone;
- 10 1-(4-Fluoro-phenyl)-2-[4-(6-methoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 1-(4-Fluoro-phenyl)-2-[(*R*)-3-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 15 1-(4-Fluoro-phenyl)-2-[4-(1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- {(*R*)-4-[2-(4-Fluoro-phenyl)-ethyl]-2-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone;
- 2-[4-(6-Bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
- 2-[4-(6-Bromo-1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
- 20 {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone;
- {(S)-4-[2-(4-Fluoro-phenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone;
- 2-[4-(5-Bromo-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
- 25 1-(4-Fluoro-phenyl)-2-[4-(6-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 2-{4-[1-(4-Fluoro-benzoyl)-1*H*-indazole-3-carbonyl]-piperazin-1-yl}-1-(4-fluoro-phenyl)-ethanone;
- {4-[2-(4-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone;
- 30 1-(4-Fluoro-phenyl)-2-[4-(6-trifluoromethoxy-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 1-(4-Fluoro-phenyl)-2-[4-(1-propyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 1-(4-Fluoro-phenyl)-2-[4-(6-*o*-tolyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
- 2-[4-(1-Benzenesulfonyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
- 35 {(*R*)-4-[2-(4-Fluoro-phenyl)-ethyl]-3-methyl-piperazin-1-yl}-(1*H*-indazol-3-yl)-methanone;

- 1-(4-Fluoro-phenyl)-2-[4-(5-o-tolyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-2-methyl-2*H*-indazole-6-carbonitrile;
{4-[2-(3-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-
5 methanone;
1-(4-Fluoro-phenyl)-2-[4-(6-methoxy-1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
{4-[2-(2-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-
methanone;
10 1-(4-Chloro-phenyl)-2-[4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
3-{4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile;
{4-[2-(2-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-
15 methanone;
3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1-methyl-1*H*-indazole-6-carbonitrile;
(6-Bromo-1-methyl-1*H*-indazol-3-yl)-{4-[2-(2,4-difluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone;
20 1-(4-Fluoro-phenyl)-2-[(*R*)-2-methyl-4-(1-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
(6-Bromo-1-methyl-1*H*-indazol-3-yl)-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone;
(1-Ethyl-1*H*-indazol-3-yl)-{4-[2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-methanone;
25 {4-[2-Fluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone;
2-[4-(5,6-Dichloro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
1-(4-Fluoro-phenyl)-2-[4-(5-methyl-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;
30 3-{4-[2-(4-Fluoro-phenyl)-ethyl]-piperazine-1-carbonyl}-1*H*-indazole-6-carbonitrile;
{4-[2,2-Difluoro-2-(4-fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone;
2-[4-(5,6-Difluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;
35 {4-[2-(2,4-Difluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone;

{4-[2-(4-Chloro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-methanone;

2-[4-(5-Fluoro-1*H*-indazole-3-carbonyl)-piperazin-1-yl]-1-(4-fluoro-phenyl)-ethanone;

1-(4-Fluoro-phenyl)-2-[4-(2-methyl-2*H*-indazole-3-carbonyl)-piperazin-1-yl]-ethanone;

5 and

{4-[2-(3-Fluoro-phenyl)-ethyl]-piperazin-1-yl}-(1-methyl-1*H*-indazol-3-yl)-

methanone;

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

- 10 24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 and a pharmaceutically acceptable carrier.
25. A method for treating a 5-HT_{2A} mediated disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 15 26. The method according to claim 25, wherein said 5-HT_{2A} mediated disorder is selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, and atrial fibrillation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 20 27. A method for treating a sleep disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 25 28. The method according to claim 27, wherein said sleep disorder is a dyssomnia.
- 30 29. The method according to claim 27, wherein said sleep disorder is insomnia.
30. The method according to claim 27, wherein said sleep disorder is a parasomnia.
- 35 31. A method for increasing slow wave sleep in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound

according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.

- 5 32. A method for improving sleep consolidation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 10 33. A method for improving sleep maintenance in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 15 34. A method for treating a condition associated with platelet aggregation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 20 35. A method for reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 25 36. A method for reducing the risk of blood clot formation in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 30 37. A method for reducing the risk of blood clot formation in an individual suffering from atrial fibrillation, comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
- 35 38. A method for treating a diabetic-related disorder in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.

39. A method for treating progressive multifocal leukoencephalopathy in an individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
40. A method for treating hypertension in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
41. A method for treating pain in an individual comprising administering to the individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
42. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a sleep disorder.
43. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a dyssomnia.
44. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of insomnia.
45. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a parasomnia.
46. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for increasing slow wave sleep.
47. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for improving sleep consolidation.
48. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for improving sleep maintenance.
49. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder.

50. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a 5-HT_{2A} mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation.
51. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a condition associated with platelet aggregation.
52. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the reduction of the risk of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof a therapeutically effective amount of a compound according to any one of claims 1 to 23 or a pharmaceutical composition according to claim 24.
53. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual.
54. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the reduction of the risk of blood clot formation in an individual suffering from atrial fibrillation.
55. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of a diabetic-related disorder.
56. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of progressive multifocal leukoencephalopathy.
57. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of hypertension.
58. Use of a compound according to any one of claims 1 to 23 for the manufacture of a medicament for the treatment of pain.
59. A compound according to any one of claims 1 to 23 for use in a method of treatment of the human or animal body by therapy.

60. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a 5-HT_{2A} mediated disorder in the human or animal body by therapy.
- 5 61. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a 5-HT_{2A} mediated disorder selected from the group consisting of coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke and atrial fibrillation in the human or animal body by therapy.
- 10 62. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a sleep disorder in the human or animal body by therapy.
63. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a dyssomnia in the human or animal body by therapy.
- 15 64. A compound according to any one of claims 1 to 23 for use in a method for the treatment of insomnia in the human or animal body by therapy.
65. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a parasomnia in the human or animal body by therapy.
- 20 66. A compound according to any one of claims 1 to 23 for use in a method for increasing slow wave sleep in the human or animal body by therapy.
- 25 67. A compound according to any one of claims 1 to 23 for use in a method for improving sleep consolidation in the human or animal body by therapy.
68. A compound according to any one of claims 1 to 23 for use in a method for improving sleep maintenance in the human or animal body by therapy.
- 30 69. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a condition associated with platelet aggregation in the human or animal body by therapy.
- 35 70. A compound according to any one of claims 1 to 23 for use in a method of reducing the risk of blood clot formation in an angioplasty or coronary bypass surgery individual by therapy.

71. A compound according to any one of claims 1 to 23 for use in a method of reducing the risk of blood clot formation in an individual by therapy.
- 5 72. A compound according to any one of claims 1 to 23 for use in a method of reducing the risk of blood clot formation in an individual suffering from atrial fibrillation by therapy.
73. A compound according to any one of claims 1 to 23 for use in a method for the treatment of a diabetic-related disorder in the human or animal body by therapy.
- 10 74. A compound according to any one of claims 1 to 23 for use in a method for the treatment of progressive multifocal leukoencephalopathy in the human or animal body by therapy.
- 15 75. A compound according to any one of claims 1 to 23 for use in a method for the treatment of hypertension in the human or animal body by therapy.
76. A compound according to any one of claims 1 to 23 for use in a method for the treatment of pain in the human or animal body by therapy.
- 20 77. A process for preparing a composition comprising admixing a compound according to any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

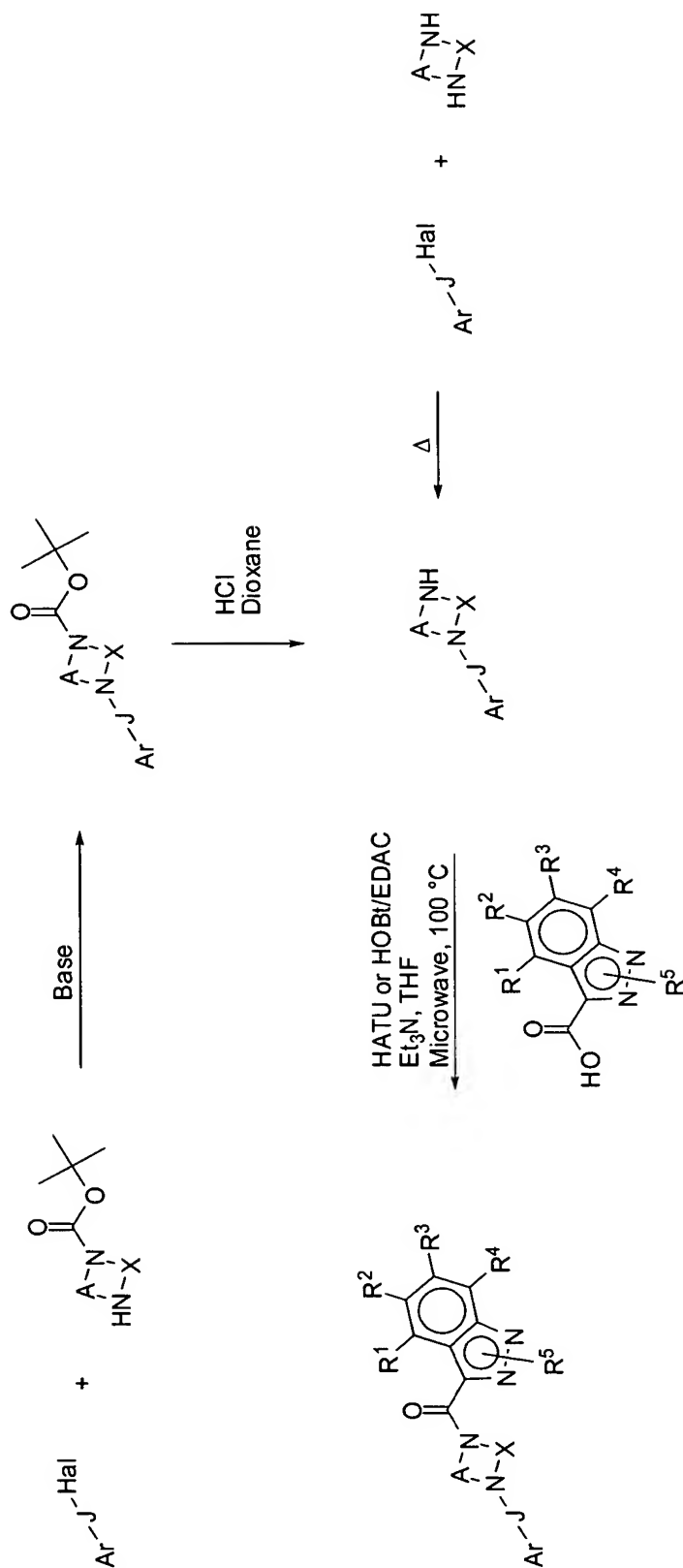


Figure 1

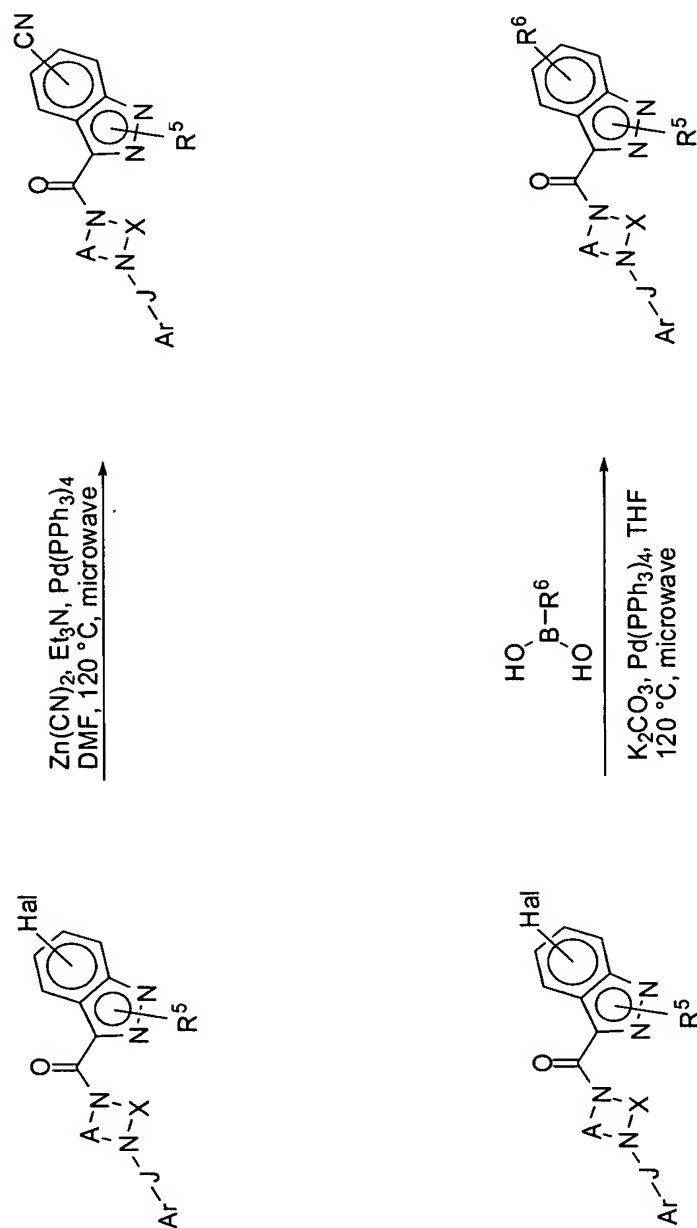
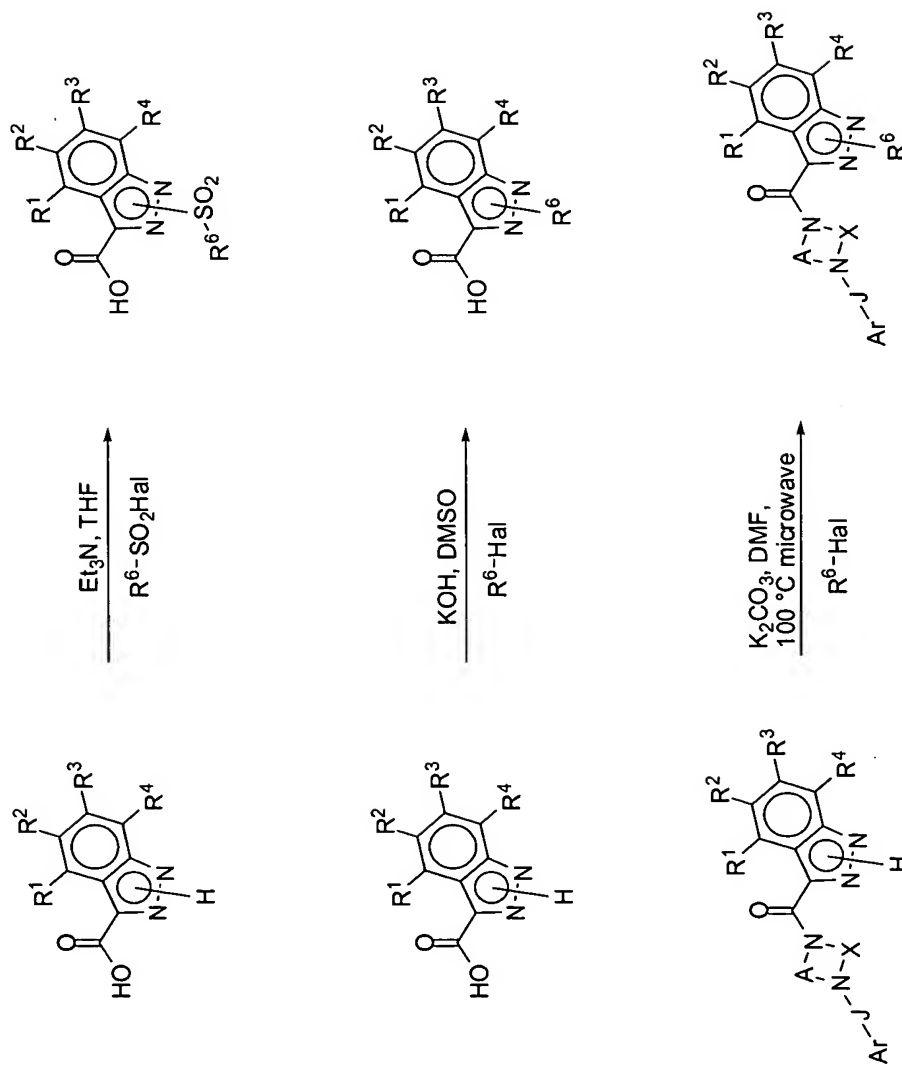


Figure 2

**Figure 3**

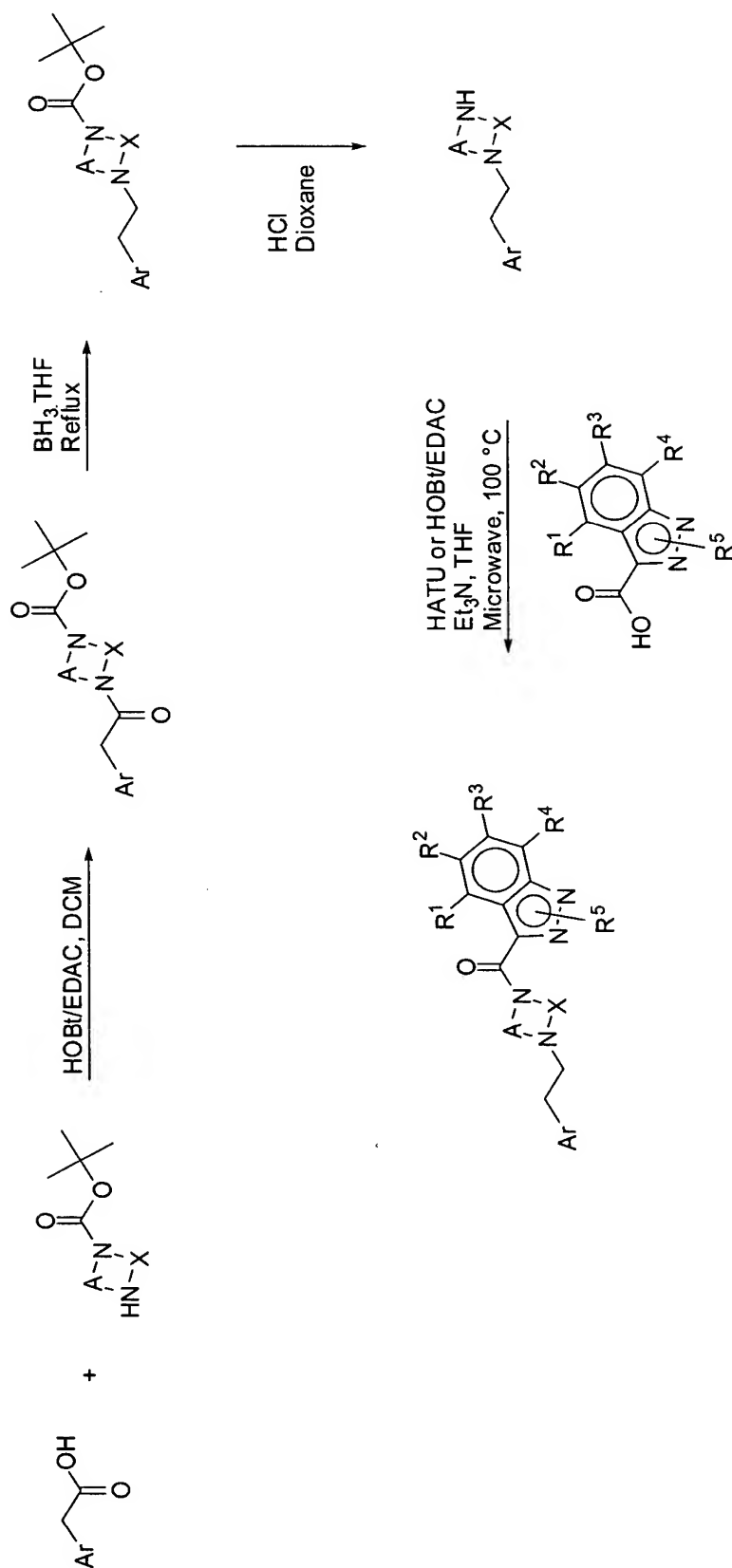
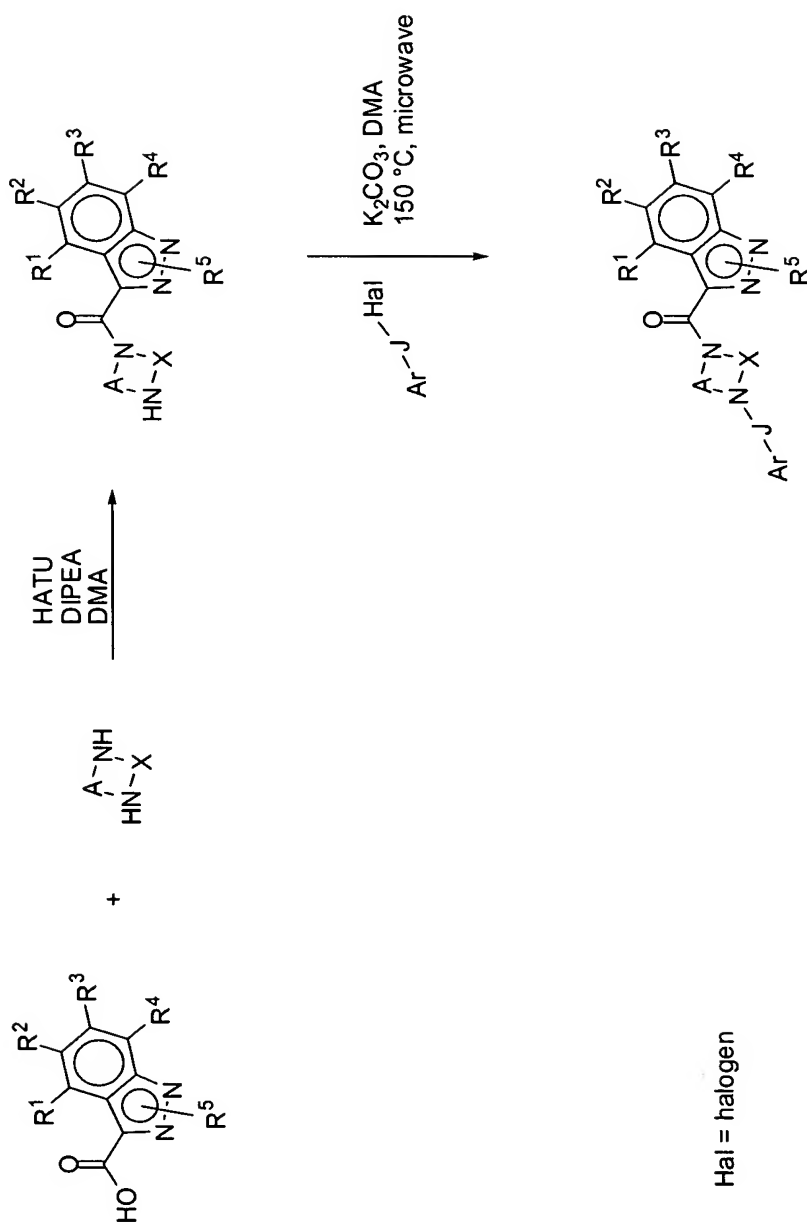
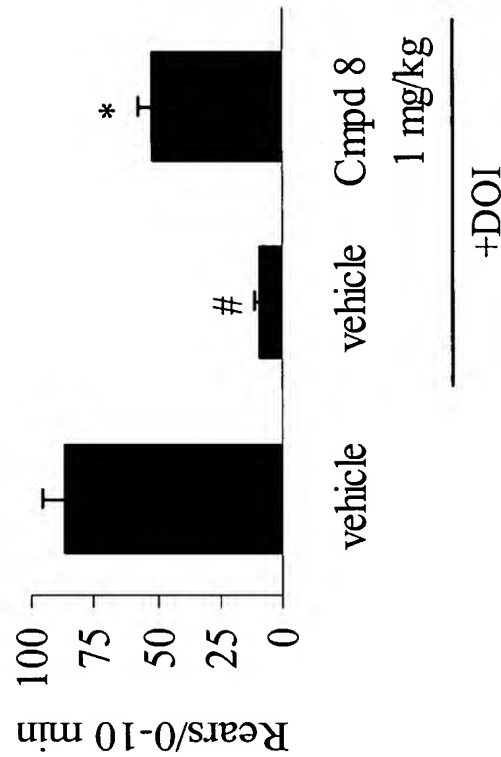


Figure 4

**Figure 5**

Attenuation of DOI-induced hypolocomotion in rats

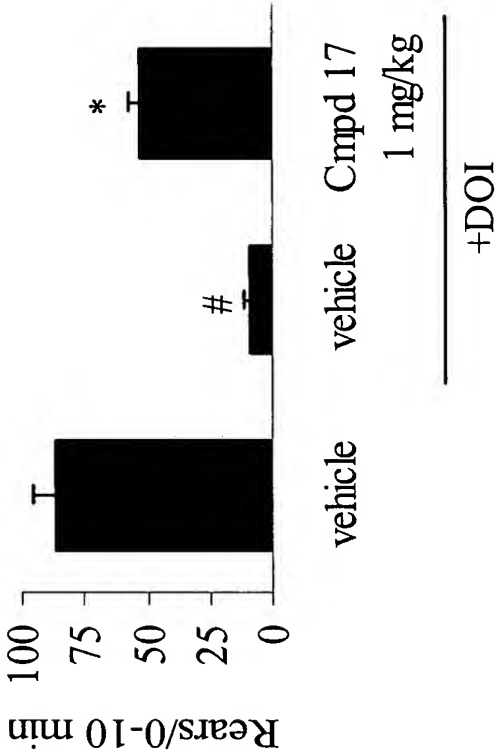


P<0.01 vs vehicle/saline

*P<0.01 vs vehicle/DOI

Figure 6

Attenuation of DOI-induced hypolocomotion in rats



P<0.01 vs vehicle/saline

*P<0.01 vs vehicle/DOI

Figure 7

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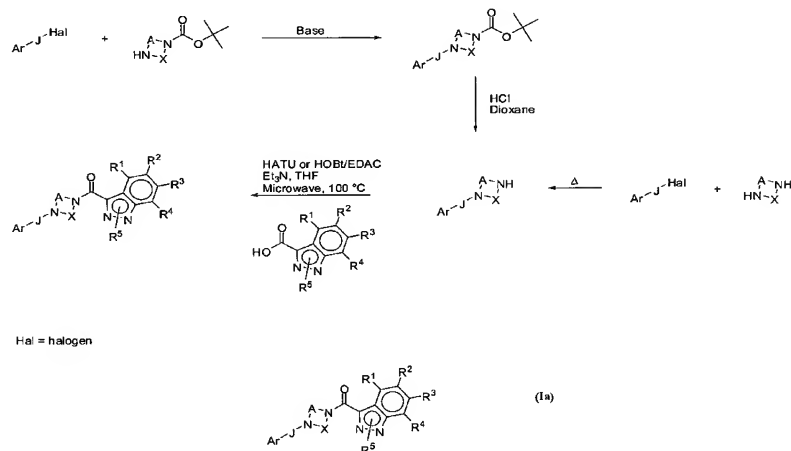
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[Continued on next page]

(54) Title: INDAZOLE DERIVATIVES AS MODULATORS OF THE 5-HT_{2A} SEROTONIN RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO



(57) Abstract: Indazole derivatives of Formula (Ia) and pharmaceutical compositions thereof that modulate the activity of the serotonin 5HT_{2A} receptor. Formula (Ia) Compounds and pharmaceutical compositions thereof are directed to methods useful in the treatment of insomnia and related sleep disorders, platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, reducing the risk of blood clot formation, asthma or symptoms thereof, agitation or symptoms thereof, behavioral disorders, drug induced psychosis, excitative psychosis, Gilles de la Tourette's syndrome, manic disorder, organic or NOS psychosis, psychotic disorders, psychosis, acute schizophrenia, chronic schizophrenia, NOS schizophrenia and related disorders, diabetic-related disorders, progressive multifocal leukoencephalopathy and the like. The present invention also relates to the methods for the treatment of 5-HT_{2A} serotonin receptor mediated disorders in combination with other pharmaceutical agents administered separately or together.



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Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/055734 A (ARENA PHARM INC [US]; TEEGARDEN BRADLEY [US]; XIONG YIFENG [US]; STRAH) 26 May 2006 (2006-05-26) the whole document	1-77
A	WO 2004/041793 A (WARNER LAMBERT CO [US]; CHO STEPHEN SUNG YONG [US]; DAVIS JAMIE MARIE) 21 May 2004 (2004-05-21) claims 1,9-15; examples 504,506,508,510	1-77
E	WO 2008/042388 A (ARENA PHARM INC [US]; XIONG YIFENG [US]; CHERRIER MARTIN C [US]; CHOI) 10 April 2008 (2008-04-10) the whole document	1-77



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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